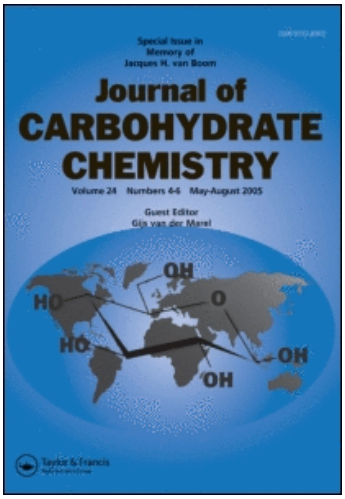

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Premanand Ramrao Patil[a]; K.P. Ravindranathan Kartha[a]
[a] Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Punjab, India

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Solvent-Free Mechanochemical Synthesis of Aryl Glycosides[1]

Premanand Ramrao Patil and K.P. Ravindranathan Kartha

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, S.A.S. Nagar, Punjab 160 062, India

Aryl glycosides have been prepared from a range of readily available glycosyl halides by a solvent-free mechanochemical procedure employing a planetary ball mill in excellent yields. Besides being a solvent-free reaction, the procedure has been successful in eliminating the need for employing any phase-transfer catalyst in the reaction.

Keywords Aryl glycoside synthesis; Mechanochemical reactions; Chemistry by ball milling; Solvent-free synthesis

INTRODUCTION

Aryl glycosides are of significant importance to both chemists and biologists because of their medicinal properties, because of their widespread occurrence in nature, and because they serve as suitable substrates in various enzyme assays.[2] They are useful in carbohydrate-lectin interaction studies[3] (serving as inhibitors) and serve as building blocks in oligosaccharide synthesis as well as substrates for the synthesis of *C*-glycosidic compounds by rearrangement.[4] A number of methods are available for their syntheses,[5] but the one employing phase-transfer catalysis is perhaps the most convenient besides being the most widely used in recent times.[3,6] However, the method often suffers from drawbacks such as β-elimination and hydrolysis, leading to a decrease in yields of the reaction.[6e] In view of our recent findings[7] that facile regioselective tritylation of various hexosides and nucleosides as well as displacement of anomeric halides by inorganic azides can be done under solvent-free conditions in a commercially available planetary ball mill, an investigation of the

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Address correspondence to K.P. Ravindranathan Kartha, Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, S.A.S. Nagar, Punjab 160 062, India. E-mail: rkartha@niper.ac.in

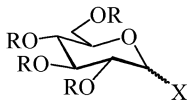
mechanochemical glycosylation of phenol and substituted phenols was initiated using acetylated glycosyl halides as glycosyl donors under solvent-free conditions without the aid of phase-transfer catalyst. The results are summarized below.

RESULTS AND DISCUSSION

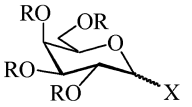
When a mixture of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**1**, 1 mmol), phenol (2 mmol), and K_2CO_3(2.2 mmol) was allowed to mix in a planetary ball mill at 400 rpm for 45 min, complete disappearance of the bromide **1** occurred and a product identical (TLC: eluent, EtOAc:*n*-Hex = 2:3) to authentic **2**[6e] was formed. Aqueous workup gave, without recourse to chromatography, crystals of **2** (yield, 85%; recrystallization from Et_2O:*n*-Hex), the structure of which was confirmed by ^1H and ^{13}C NMR spectroscopy (entry 1, Table 1). In sharp contrast to the observations reported by Dess et al.[6e] (as well as others as reported by them), it was interesting to note that no by-products arising out of the possible β-elimination and/or hydrolysis (to lead to **3** and **4**, respectively) were detected in the reaction mixture. The present method was also seen to be faster as well as more efficient in terms of the yield observed.

Experiments with other alkali metal carbonates as possible substitutes for K_2CO_3 proved less successful (results not shown in the table). Thus, the Na_2CO_3-assisted reactions (at 400 rpm for 48 hr) were shown to be considerably slower as a result of which the desired phenyl glycoside **2** was obtained in poor yield (only 40%) with the hydrolytic product **4**[8] preponderating (>50%). Use of Cs_2CO_3 and KOH (at 400 rpm for 15 min), on the other hand, led to the formation of partially deacetylated products, thus giving the desired product **2** in only low yields (31% and 47%, respectively). Further, no reaction was observed in attempts with $BaCO_3$, and hence the unchanged starting material **1** was recovered. Among the organic bases tried, imidazole led to the formation of the hydrolytic product **4** (as the sole product) and DABCO to the enitol derivative **3**[9] (as the sole product).

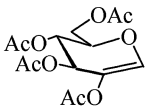
The applicability of the method using K_2CO_3 as the base was therefore further evaluated by extending the reaction to some of the other important glycosyl bromides of our specific interest. Thus, the reaction of phenol with galactosyl bromide **5** in the presence of K_2CO_3 was found to take place very efficiently at 400 rpm in the ball mill, giving the corresponding 1,2-*trans*-linked galactopyranoside **6**[6a] in 92% yield without any need for column chromatographic purification (entry 2, Table 1). The reaction was also scaled up to 5 g without affecting the yield (entry 3, Table 1). In fact, as observed in our earlier work, the multigram scale reactions were consistently more efficient than the mmol scale reactions.[7a] The glycosyl bromide **7**, a relatively more stable benzobromo analog of **5**, under similar conditions also underwent successful glycosylation reaction in 1 h, giving the desired product (**8**) in excellent yield



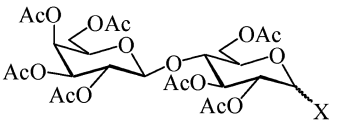
1 R = Ac, X = α-Br
2 R = Ac, X = β-OPh
4 R = Ac, X = OH
9 R = Ac, X = β-OPh-*p*-OMe
10 R = Ac, X = β-OPNP
14 R = Ac, X = β-OPh-*p*-NHAc
17 R = Ac, X = β-OPh-*p*-CHO



5 R = Ac, X = α-Br
6 R = Ac, X = β-OPh
7 R = Bz, X = α-Br
8 R = Bz, X = β-OPh
11 R = Ac, X = β-OPNP
15 R = Ac, X = β-OPh-*p*-NHBoc
16 R = Ac, X = β-OPh-*m*-NHBoc
18 R = Ac, X = β-OPh-*p*-CHO

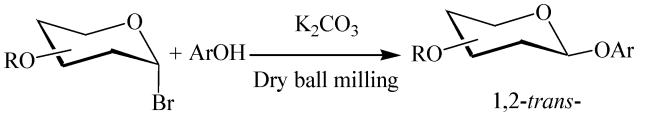


3



12 R = Ac, X = α-Br
13 R = Ac, X = β-OPNP

Table 1: Aryl-*O*-glycoside synthesis by dry ball milling[a]



1,2-*trans*-

Entry	Glycosyl bromide	Ar	Reaction time (hr)	Product (Yield, %)	Reference
1	**1**	Ph	0.75	**2** (85)	6e, 10
2	**5**	Ph	0.75	**6** (92)	6a, 6e
3[b]	**5**	Ph	0.75	**6** (95)	6a, 6e
4	**7**	Ph	1	**8** (96)	11
5	**1**	Ph-p-OMe	0.75	**9** (96)	12
6[c]	**1**	Ph-p-NO_2	6	**10** (66)	13
7	**5**	Ph-p-NO_2	6	**11** (82)	13
8[d]	**1**	Ph-p-NO_2	3	**10** (88)	13
9[d,e]	**5**	Ph-p-NO_2	1	**11** (93)	13
10[d]	**12**	Ph-p-NO_2	8	**13** (71)	3[a]
11	**1**	Ph-p-NHAc	1	**14** (82)	14
12	**5**	Ph-p-NHBoc	3	**15** (89)	—
13	**5**	Ph-m-NHBoc	3	**16** (87)	—
14	**1**	Ph-p-CHO	3	**17** (79)	15
15	**5**	Ph-p-CHO	1	**18** (81)	16

[a]Reactions were carried out with bromide (1 mmol):ArOH:K_2CO_3 in the mole ratio of 1:2:2.2 at 400 rpm and the products were isolated by crystallization after aqueous workup.
[b]The reaction was carried out with 5 g (12.16 mmol) of **5**.
[c]Yield after purification by column chromatography.
[d]Reaction was carried out with bromide (2.5 mmol):ArOH:K_2CO_3 in the mole ratio of 1:2:1.5 at 600 rpm.
[e]The reaction was also conducted on a 12-g and 25-g scale (with respect to **5**) without affecting the yields.

(96%, entry 4, Table 1). As expected, substituted phenols bearing electron donating groups were proved equally suitable as glycosyl acceptors, which was evident from the facile formation of the *p*-methoxyphenyl glucoside **9** (entry 5, Table 1) from 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**1**). Likewise, under the above conditions, and as to be expected, the relatively "disarmed"

p-nitrophenol (PNP-OH) was found to be more sluggish toward the reaction with bromides such as those described here (e.g., compare entries 1 and 2 with 6 and 7, respectively, Table 1). It also must be noted that while the reaction of PNP-OH with the relatively more reactive galactosyl bromide **5** produced only the desired 1,2-*trans*-linked glycoside (in 82% yield after recrystallization from Et_2O:*n*-Hex after a 6 h reaction at 400 rpm), formation of the corresponding glycoside (yield, 66% after chromatographic purification after a 6-hr reaction at 400 rpm) in the case of reaction with glucosyl bromide **1** was accompanied by the formation of the elimination product **4** (approx. 30% upon chromatographic isolation). It was reasoned that the formation of the by-product was at least in part, if not solely, due to the lower reactivity of the substrates. Therefore, based on our earlier observation that increasing the speed of mixing had led to considerably faster reactions,[7a] when the reaction of the bromide **1** with PNP-OH was carried out at 600 rpm, the corresponding 1,2-*trans*-linked glycoside was obtained as the sole product in 88% yield directly after crystallization following the aqueous workup (entry 8, Table 1). Here, reducing the amount of K_2CO_3 employed in the reaction was also found to be fruitful for ensuring the favored reaction as can be seen from the table. Under these conditions the galactopyranosyl bromide (**5**) also underwent complete reaction with PNP-OH in 1 h (entry 9, yield 93%), and was equally successful when carried out at preparative scale (in two separate experiments of 12-g and 25-g scale). Lactosyl bromide **12** also gave satisfactory results (71% yield, entry 10, Table 1) upon mixing under these conditions to yield the corresponding lactoside **13**. The results obtained in reactions (carried out at 400 rpm; entries 11–15, Table 1) of the *gluco*- and *galacto*-configured glycosyl bromides (**1** and **5**, respectively) with some of the other deactivated acceptors of interest to us are also reported. Results of further work in this area will be reported in due course.

CONCLUSIONS

A highly efficient practical route to aryl glycosides under solvent-free conditions, requiring neither chromatographic purification nor use of a phase-transfer catalyst, is reported for the first time in synthetic carbohydrate chemistry.

EXPERIMENTAL

All reagent chemicals were purchased from Aldrich Chemical Co. (Milwaukee, WI, USA). TLC was performed on 0.2-mm Merck precoated silica gel 60 F254 aluminum sheets. Melting points were recorded on a capillary melting point apparatus and are uncorrected; the values reported below are for crystals obtained from Et_2O-*n*-Hex unless otherwise mentioned. Specific rotations

were obtained on AUTOPOL IV polarimeter at 20°C. IR spectra were recorded on a Nicolet FT-IR Impact 410 instrument either as neat or KBr pellets. Mass spectra were obtained on an ultraflex TOF/TOF MALDI mass spectrometer, which is equipped with a reflector and controlled by the Flex control 1.4 software package. NMR spectra were recorded on a 300/400 MHz Bruker FT NMR (AVANCE^{DPX}300/AVANCE^{III}400) spectrometer at 300/400 MHz for the ^{1}H and at 75.47/100.62 MHz for the ^{13}C nuclei. Chemical shifts are reported in ppm from TMS as the internal standard. The spectral data obtained for the compounds reported here were in accordance with the expected structures.

General Procedure for the Aryl Glycoside Synthesis Using a Planetary Ball Mill

The desired glycosyl halide (see Table 1 for details; e.g., entry 3: **5**, 5g, 12.16 mmol), the desired phenol (e.g., Ph-OH, 24.33 mmol), and K_2CO_3(26.76 mmol) were allowed to mix in a stainless steel (SS, for details see ref. [7a]) jar (capacity, 50 mL) containing SS balls (10 numbers, 10 mm o.d.) in a planetary ball mill (Retsch PM-100; Retsch GmbH & Co. KG, Germany) at 400 rpm (or 600 rpm for faster reactions) until the reaction was complete (TLC, e.g., EtOAc:*n*-Hex, 2:3, 45 min for **5** and Ph-OH at 400 rpm). The mixture was then taken up in CH_2Cl_2 and was washed successively with cold dil. aq. Na_2CO_3 solution and water in a separatory funnel. The organic layer was dried (Na_2SO_4) and concentrated to dryness under reduced pressure to yield the respective glycoside which was recrystallized from a suitable solvent such as Et_2O-*n*-Hex or MeOH or EtOH as desired [e.g., **6**, 4.9 g from **5**, 95%; mp 116–117°C from Et_2O-*n*-Hex and 119–120°C from MeOH (lit.[6e] 120–122°C, solvent not known); $[\alpha]_D$+3.9 (lit.[6e] −27.6, c 2 in $CHCl_3$)].

Compounds **2** [mp 126–127 (lit.[10] 125–126); $[\alpha]_D$–22.3 (lit.[10] −22.5, c 2 in $CHCl_3$)], **6**, **8**, **9** [mp 86–87 (lit.[12] 98.5); $[\alpha]_D$–13.3 (lit.[12]–15.5, c 1 in $CHCl_3$)], **10** [mp 176–177 (lit.[13] 177–178.5); $[\alpha]_D$–31.9 (lit.[13]–38.9, c 1 in $CHCl_3$)], **11** [mp 143–144 (lit.[13] 146–147); $[\alpha]_D$–9.3 (lit.[13]–9.7, c 1 in $CHCl_3$)], **13**, **14**, **17** [mp 134–135 (lit.[15]142–143); $[\alpha]_D$–27.8 (lit.[15]–29.5, c 0.5 in $CHCl_3$)], and **18** [mp 102–103 (lit.[16] 121.5–122); $[\alpha]_D$–1.0 (lit.[16]–1.1, c 1 in CH_3OH)] have been reported before and their NMR data were in agreement with the literature values. But the NMR spectral data/physical constants for compounds **8**, **13**, and **14** were not found and therefore the data obtained in the present work have been listed below. No literature precedence for compounds **15** and **16** was found and hence their physical constants and NMR spectral data have also been listed below.

Phenyl 2,3,4,6-tetra-*O*-benzoyl-*β*-D-galactopyranoside (8)

Compound **8** was prepared by the general procedure described above in 96% yield as a colorless solid; mp 68–69°C (Et_2O:*n*-Hex); $[\alpha]_D = +139.2$ (C 1 in

$CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, 2H, $J = 7.2$ Hz, 2,6 Bz-H), 8.06 (d, 2H, $J = 7.2$ Hz, 2,6 Bz-H), 7.97 (d, 2H, $J = 7.3$ Hz, 2,6 Bz-H), 7.83 (d, 2H, $J = 7.2$ Hz, 2,6 Bz-H), 7.63–7.16 (m, 14H, 4 × 3,4,5 Bz-H, 1 × 2,6 Ph-H), 7.03 (m, 3H, 3,4,5 Ph-H), 6.07 (m, 2H, H-2, H-4), 5.69 (dd, 1H, $J_{2,3} = 10.3$ Hz, $J_{3,4} =$ 3.3 Hz, H-3), 5.39 (d, 1H, $J_{1,2} = 7.9$ Hz, H-1), 4.70 (dd, 1H,$J_{5,6a} = 7.3$, $J_{6a,,6b} =$ 11.1 Hz H-6a), 4.57–4.46 (m, 2H, H-5, H-6b); ^{13}C NMR (75.47, $CDCl_3$) δ 166.5, 166.1, 165.8, 157.6, 134.2, 133.9, 130.6, 130.3, 130.0, 129.7, 129.4, 129.2, 129.0, 128.9, 128.8, 123.9, 117.8, 100.7, 72.3, 72.2, 70.0, 68.5, 62.8.

4-Nitrophenyl 4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (13)

Compound **13** was prepared by the general procedure described above in 71% yield as a colorless solid; mp 106–107°C (Et_2O:*n*-Hex); $[\alpha]_D = -23.3$ (c 1 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, 2H, $J = 9.1$Hz, 3,5 Ph-H), 7.07 (d, 2H, $J = 7.2$ Hz, 2,6 Ph-H), 5.37 (d, 1H, $J_{3,4} = 2.8$ Hz, H-4′), 5.33–5.10 (m, 4H, H-3, H-2′, H-2, H-1), 4.99 (dd, 1H, $J_{2,3} = 10.3$ Hz, H-3′), 4.51 (m, 2H, H-1′, H-6a), 4.24–4.11 (m, 3H, H-6b, H-6a′, H-6b′), 3.94–3.86 (m, 3H, H-4, H-5, H-5′), 2.16 (s, 3H, $COCH_3$), 2.12–2.06 (m, 15H, 5 × COCH3), 1.97 (s, 3H, $COCH_3$); ^{13}C NMR (75.47, $CDCl_3$) δ 170.9, 170.6, 170.2, 170.0, 169.6, 161.7, 143.7, 126.3, 117.1, 101.7, 98.3, 76.5, 73.6, 73.1, 71.7, 71.4, 71.3, 69.6, 67.1, 62.4, 61.3, 21.2, 21.1, 21.0.

4-*N*-Acetylaminophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (14)

Compound **14** was prepared by the general procedure described above in 82% yield as a colorless solid; mp 110–111°C (Et_2O:*n*-Hex); $[\alpha]_D = -11.7$ (c 1 in $CHCl_3$);^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 2H, $J = 8.8$ Hz, 3,5 Ph-H), 7.03 (d, 2H, $J = 8.8$ Hz, 2,6 Ph-H), 5.26 (m, 2H, H-2, H-3), 5.18 (d, 1H, $J_{3,4} =$ 9.6 Hz, H-4), 5.02 (d, 1H, $J_{1,2} = 7.2$ Hz, H-2), 4.29 (dd, 1H,$J_{5,6a} = 5.6$, $J_{6a,,6b}$ 12.4 H-6a), 4.14 (dd, 1H,$J_{5,6a} = 2.4$ Hz, H-6b), 3.83 (ddd, 1H, H-5), 2.16, 2.10, 2.08, 2.06, 2.04 (5s, 15H, *N*-$COCH_3$, 4 × $COCH_3$); ^{13}C NMR (100.62 MHz,$CDCl_3$) δ 170.6, 170.2, 169.6, 169.4, 168.3, 153.4, 135.6, 121.9, 117.6, 99.5, 72.1, 72.0, 71.1, 68.2, 61.9, 24.4, 21.0, 20.6, 20.5.

4-*tert*-Butoxycarbonylaminophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (15)

Compound **15** was prepared by the general procedure described above in 89% yield as a colorless solid; mp 156–157°C (Et_2O:*n*-Hex); $[\alpha]_D = +4.7$ (c 1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, 2H, $J = 8.4$ Hz, 3,5 Ph-H),

6.95 (dd, 2H, $J = 6.8$, $J = 2.0$ Hz 1.5 Hz, 2,6 Ph-H), 6.42 (bs, 1H, NH), 5.45 (m, 2H, H-2, H-4), 5.10 (dd, 1H, $J_{2,3} = 10.4$ Hz, $J_{3,4} = 3.2$ Hz, H-3), 4.96 (d, 1H, $J_{1,2} = 7.6$ Hz, H-1), 4.18 (m, 2H, H-6a, H-6b), 4.02 (t, 1H, H-5), 2.18, 2.07, 2.05, 2.01 (4s, 12H, 4 × $COCH_3$), 1.50 (s, 9H, ^{t}Bu); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 170.3, 170.2, 170.1, 169.3, 152.9, 133.8, 120.1, 117.8, 115.5, 100.3, 80.5, 71.0, 70.8, 68.7, 66.9, 61.3, 28.3, 20.7, 20.6, 20.5; MALDI-TOF MS $C_{25}H_{33}NO_{12}$ $[M]^+$ calcd. m/z 539.539, found m/z 578.759 ($M+K^+$), 562.770 ($M+Na^+$), 331.519 $(M\text{-}OPhNHBoc)^+$.

3-*tert*-Butoxycarbonylaminophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (16)

Compound **16** was prepared by the general procedure described above in 87% yield as a colorless solid; mp 117–118°C (Et_2O:*n*-Hex); $[\alpha]_D = +7.3$ (c 1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (m, 2H, 2,5 Ph-H), 7.01 (d, 1H, $J = 7.9$ Hz, 6-Ph-H), 6.68 (d, 1H, $J = 7.9$ Hz, 4-Ph-H), 6.50 (bs, 1H, NH), 5.45 (m, 2H, H-2, H-4), 5.08 (m, 2H, H-3, H-1), 4.18 (m, 2H, H-6a, H-6b), 4.06 (t, 1H,$J_{5,6a} = 6.4$, H-5), 2.18, 2.05, 2.04, 2.00 (4s, 12H, 4 × $COCH_3$), 1.50 (s, 9H, ^{t}Bu); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 170.9, 170.8, 170.6, 169.9, 158.0, 152.9, 140.2, 130.3, 113.8, 111.9, 107.9, 100.0, 81.2, 71.5, 71.4, 69.2, 67.4, 61.8, 28.8, 21.2, 21.18, 21.16; MALDI-TOF MS $C_{25}H_{33}NO_{12}$ $[M]^+$ calcd. m/z 539.539, found m/z 578.863 ($M+K^+$), 562.874 ($M+Na^+$), 331.588 $(M\text{-}OPhNHBoc)^+$.

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