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Homogeneous azidophenylselenylation of glycals using $TMSN_3$–Ph_2Se_2–$PhI(OAc)_2$

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Abstract—An improved preparative method for homogeneous azidophenylselenylation of glycals is described consisting of reaction with $TMSN_3$ and Ph_2Se_2 in the presence of $PhI(OAc)_2$. The use of $TMSN_3$ instead of NaN_3 as in the heterogeneous procedure, allowed both a reduced reaction time and a scale-up that was not possible in the case of the azidophenylselenylation of substituted glycals using NaN_3.

Complex carbohydrate chains of natural glycolipid[1] and glycoprotein[2] conjugates often contain the 2-amino-2-deoxy-α-D-galactopyranoside unit. The most convenient synthesis of such structures uses appropriately substituted 2-azido-2-deoxy-galactosyl donors. Among different methods for their preparation the azidonitration of triacetylgalactal **1** has been used most widely.[3] However, this method is laborious and also needs extra steps for the transformation of nitrate adduct **A** (Scheme 1) into glycosyl donor **B** bearing the leaving group X, which is required for efficient glycosylation. Thus the development of alternative, more practical, and shorter routes to 2-azido-2-deoxy-galactosyl donors is desirable.

Tingoli and co-workers described the anti-Markovnikov one-step azidophenylselenylation (APS) of olefins including tri-*O*-methyl-D-glucal by treatment with a mixture of NaN_3, $PhI(OAc)_2$, and Ph_2Se_2.[4] This method was applied by Czernecki et al.[5] and with a small variation of reagent ratio by the Santoyo-Gonzales et al.[6] for the transformation of galactal **1** into phenyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-1-seleno-α-D-galactopyranoside **2** in yields of 70–90%.

Selenoglycosides were shown[7] to be efficient glycosyl donors and thus the one-step APS transformation of glycals can be seen as an advantageous method for the synthesis of 2-azido-glycosyl donors when compared with the azidonitration procedure. Accordingly we intended to apply the APS reaction for the preparation of selenoglycoside **2** and its derivatives, to be used in the synthesis of Tn-antigen and blood group A related oligosaccharide chains.

Unfortunately our attempts to reproduce published protocols for the preparation of selenoglycoside **2** were unsuccessful. Thus, using 0.25 M of substrate **1** according to Czernecki et al.[5] we observed the formation of only traces of selenoglycoside **2** along with many by-products (Table 1, entry 1). When the concentration of substrate **1** was lowered to 0.04 M according to Santoyo-Gonzales et al.[6] we obtained the desired product **2** together with its minor *talo*-isomer **3** in a good overall yield of 88% on a 0.1 g scale (entry 2) but only in 53% on a 2 g scale (entry 3). The lower efficiency could be explained by the heterogeneity of the reaction media due to the insolubility of sodium azide in dichloromethane, which complicates the generation of azide radicals, formation of which is the initial step in the proposed mechanism for the heterogeneous APS reaction.[4]

To overcome this problem we investigated the possibility of using a soluble azide donor, namely trimethylsilyl azide ($TMSN_3$). We found that treatment of a solution of triacetylgalactal **1**, Ph_2Se_2, and $PhI(OAc)_2$ in dichloromethane with $TMSN_3$ under typical conditions[8] gave, in 4 h, a 9:1:1 mixture of target adduct **2**, its regioisomer **3** and bis-azide **4** in a total yield of 92% (entry 4). Pure selenoglycoside **2** could be easily obtained after

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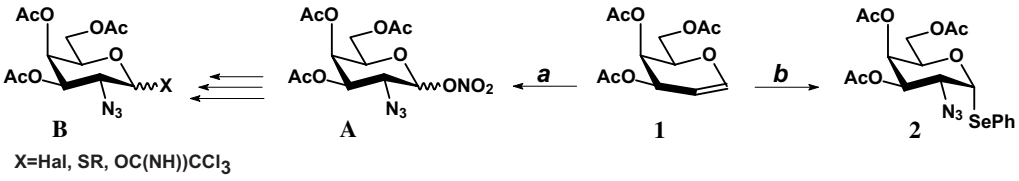
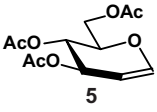
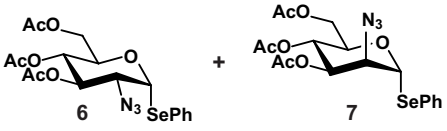
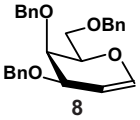
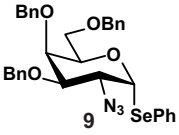
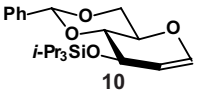
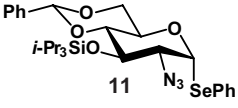
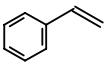
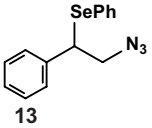
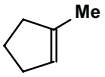
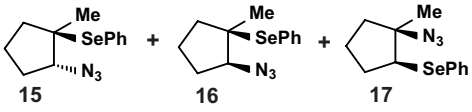
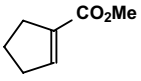
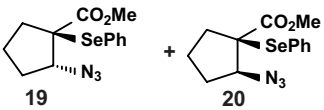


Scheme 1. The synthesis of 2-azido-2-deoxy-galactosyl donors from galactal **1** using azidonitration[3] (a) and one-step APS (b) protocols.

Table 1. APS under homogeneous conditions: a typical procedure for entries 4–9 is described in Ref. 8

Entry	Olefin substrate	Azide donor	Reaction time (h)	Products	Yield (product ratio)
1[a]	**1**	NaN_3	48	**2**	5%
2[b]	**1** (0.1 g)	NaN_3	48	**2** + **3**	88% (**2**:**3** = **10**:**1**)
3[b]	**1** (2 g)	NaN_3	144	**2** + **3**	53% (**2**:**3** = **10**:**1**)
4	**1**	$TMSN_3$	4	**2** + **3** + **4**	92% (**2**:**3**:**4** = 9:1:1)
5	 **5**	$TMSN_3$	4	 **6** + **7**	91% (**6**:**7** = 8:3)
6	 **8**	$TMSN_3$	2.5	 **9**	72%
7	 **10**	$TMSN_3$	3.5	 **11**	77%
8	 **12**	$TMSN_3$	2	 **13**	92%
9	 **14**	$TMSN_3$	4	 **15** **16** **17**	73% (**15**:**16**:**17** = 10:3:1)
10	 **18**	$TMSN_3$	2	 **19** **20**	69% (**18**:**19** = 3:1)

[a] This experiment was performed under the conditions of Ref. 5, where yields of 70–92% for adduct **2** were reported.
[b] This experiment was performed under the conditions of Ref. 6, where a yield of 91% for adduct **2** was reported.

crystallization of this mixture from *i*-PrOH. This APS transformation of galactal **1** can be reproduced at 5 g and larger scales with the same result.

Treatment of triacetylglucal **5**, also for 4 h under the same conditions, gave 91% of an inseparable 8:3 mixture of *gluco*- and *manno*-adducts **6** and **7** (entry 5). Similarly, from tri-*O*-benzyl-galactal **8** and 4,6-*O*-benzylidene-3-*O*-tri(isopropyl)silyl-D-glucal **10**, the selenoglycosides **9** and **11** were obtained in 72% and 77% yields, respectively (entries 6 and 7). Thus the homogeneous APS reaction is useful for the transformation of substrates

containing benzyl and benzylidene groups which were reported[5,6] to be unstable under the conditions of the heterogeneous APS reaction. In particular, the low yield in the preparation of selenide **9** from **8** under heterogeneous conditions was explained by the low stability of the nonacyl *O*-blocking groups in the presence of azide radicals in the reaction media.[5,6]

It is noteworthy that the APS transformation of tribenzylgalactal **8** under homogeneous conditions proceeds slightly faster than that of its triacetyl analog **1** (entries 4 and 6). Additionally, the APS reaction under homogeneous conditions proceeds not only with higher yield but also much more rapidly (2–4 h) than the heterogeneous one (several days).[5,6,9] Reaction of silylated glucal **10** was not accompanied by the formation of enone side products, which were observed when 3-*O*-silylated glucal derivatives were treated with $PhI(OAc)_2$ and $TMSN_3$ but in the absence of Ph_2Se_2.[10]

The APS reaction with the use of $TMSN_3$ can be applied to the transformation of noncarbohydrate olefins as well. Thus styrene **12** gave anti-Markovnikov adduct **13** exclusively (entry 8) whereas methylcyclopentene **14** gave the adduct **15** with smaller amounts of its isomers **16** and **17** (entry 9). The transformation of the electron-deficient alkene **18** also proceeded effectively and regiospecifically to give isomeric 2-azido-1-phenylseleno-adducts **19** and **20** (entry 10).

In conclusion, we have demonstrated the advantageous use of $TMSN_3$ instead of NaN_3 in APS reactions in providing shorter reaction times and reliable scale-ups. Substrate specificity in the APS transformation of glycals with regard to their stereochemistry and blocking groups as well as a study of the mechanism of the homogeneous APS reaction and uses of the phenyl 2-azido-2-deoxy-1-selenoglycosides prepared in α- and β-glycosylation reactions will be reported elsewhere.

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8. Typical procedure: The solution of alkene (1 mmol) and Ph_2Se_2 (1 mmol) in CH_2Cl_2 (5 ml) was cooled to −30 °C under argon and $PhI(OAc)_2$ (1 mmol) and $TMSN_3$ (2 mmol) were added sequentially. After stirring for 5 min the flask was sealed and was placed in a freezer at a constant temperature of −10 °C. When the conversion of starting material was completed (TLC: Silica Gel 60 F254 (E. Merck, Darmstadt, Germany), eluent petroleum ether–toluene (1:2) for compounds **8**, **10**, **12** and **14** or ethyl acetate–toluene (1:5) for compounds **1** and **5**) the reaction mixture was warmed to room temperature, the solvent was evaporated and the resulting solid was subjected to column chromatography (Silica Gel 60 (E. Merck, Darmstadt, Germany), gradient elution from petroleum ether to ethyl acetate). The structures of the products of APS reactions (Table 1) were assessed using ^1H (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) spectroscopy. NMR data for compounds **2**, **4**, **6**, **7** and **13** were in good agreement with published data. Mixtures of compounds **15**, **16** and **17** and of **19** and **20** were not separated because of their instability and partial decomposition within several days even if stored at −20 °C. Selected NMR data for new compounds: **3**: ^1H NMR: 7.55 (d, 2H, *o*-Ph, $J = 7.4$ Hz), 7.30–7.40 (m, 3H, *m*- and *p*-Ph), 5.72 (br s, 1H, H-1), 5.37 (m, 2H, H-3 and H-4), 4.41(br d, 1H, H-5, $J_{5,6} = J_{5,6'} = 6.5$ Hz), 4.22 (d, 2H, H-6 and H-6′, $J_{6,5} = J_{6',5} = 6.5$ Hz), 3.44 (br d, 1H, H-2, $J_{2,3} = 5.0$ Hz), 2.23, 2.11, 2.08 (3s, 9H, Ac); ^{13}C NMR: 169.5–170.0 (C═O), 128.1–136.6 (Ar), 91.5 (C-1), 69.2 (C-5), 66.6 (C-3), 66.0 (C-4), 61.8 (C-6), 45.8 (C-2), 20.5–20.7 (*Me*C═O). **11**: ^1H NMR: 7.10–7.80 (10H, m, Ar), 5.95 (1H, d, H-1, $J_{1,2} = 5.4$ Hz), 5.50 (1H, s, PhCH), 4.35 (1H, m, H-5), 4.17 (1H, dd, H-6, $J_{6,5} = 4.9$ Hz, $J_{6,6'} = 11.7$ Hz), 4.12 (1H, t, H-3, $J_{3,2} = J_{3,4} = 9.3$ Hz), 3.84 (1H, dd, H-2, $J_{1,2} = 5.4$ Hz, $J_{2,3} = 9.3$ Hz), 3.80 (1H, br d, H-6, $J_{6',6} = 11.7$ Hz), 3.58 (1H, t, H-4, $J_{4,3} = J_{4,5} = 9.2$ Hz) 1.05 (21H, m, *i*-Pr); ^{13}C NMR: 137.6 (*ipso*-Ph), 126.7–131.0 (Ar), 102.6 (Ph*C*H), 85.3 (C-1), 82.2 (C-4), 72.6 (C-3), 68.5 (C-6), 67.1 (C-2), 65.5 (C-5), 18.1, 12.9. **15**: ^1H NMR ($CDCl_3$), δ: 7.72 (2H, d, *o*-Ph, $J = 7.3$ Hz), 7.40 (3H, m, *p*- and *m*-Ph), 3.86 (1H, dd, H-2, $J = 3.2$ Hz and $J = 6.8$ Hz), 2.37 (1H, m, H-3), 1.92 (2H, m, H-5, H-5′), 1.83 (3H, m, H-3′, H-4, H-4′), 1.56 (3H, s, CH_3); ^{13}C NMR, δ: 137.9 (*ipso*-Ph), 127.1–129.3 (Ph), 70.4 (C-2), 56.0 (C-1), 38.2 (C-5), 29.6 (C-3), 23.4 (CH_3), 21.1 (C-4). **16**: ^1H NMR ($CDCl_3$), δ: 7.74 (2H, d, *o*-Ph, $J = 7.5$ Hz), 7.40 (3H, m, *p*- and *m*-Ph), 3.70 (1H, t, H-2, $J = 7.7$ Hz), 2.18 (1H, m, H-3), 2.11 (1H, m, H-3′), 1.95 (1H, m, H-4), 1.70 (1H, m, H-4′), 1.57 (2H, m, H-5, H-5′), 1.56 (3H, s, CH_3); ^{13}C NMR, δ: 138. 1 (*ipso*-Ph), 127.1–129.3 (Ph), 72.1 (C-2), 58.1 (C-1), 38.0 (C-5), 29.3 (C-3), 28.0 (CH_3), 20.1 (C-4). **17**: ^1H NMR ($CDCl_3$), δ: 7.30–7.90 (5H, m, Ar), 3.62 (1H, t, H-2, $J = 7.5$ Hz), 2.33 (2H, m, H-3, H-3′), 1.95 (1H, m, H-4), 1.79 (2H, m, H-5, H-5′), 1.61 (1H, m, H-4′), 1.52 (3H, s, CH_3); ^{13}C NMR, δ: 137.7 (*ipso*-Ph), 127.1–129.3 (Ph), 64.8

(C-1), 52.8 (C-2), 36.2 (C-5), 32.2 (C-3), 24.3 (C-4), 21.7 (CH_3). **19**: ^{1}H NMR ($CDCl_3$), δ: 7.59 (2H, d, *o*-Ph, J = 7.4 Hz), 7.42 (1H, t, *p*-Ph, J = 7.5 Hz), 7.35 (2H, t, *m*-Ph, J = 7.4 Hz), 3.97 (1H, d, H-2, J = 5.5 Hz), 3.70 (3H, s, OMe), 2.51 (1H, m, H-3), 2.30 (1H, m, H-5), 1.91 (1H, m, H-3′), 1.88 (2H, m, H-4, H-4′), 1.85 (1H, m, H-5′); ^{13}C NMR, δ: 172.0 (C═O), 137.5 (*ipso*-Ph), 126.8–129.7 (Ph), 69.1 (C-2), 59.9 (C-1), 51.9 (OMe), 31.1 (C-5), 30.0 (C-3), 20.7 (C-4). **20**: ^{1}H NMR ($CDCl_3$), δ: 7.63 (2H, d, *o*-Ph, J = 7.5 Hz), 7.50 (1H, t, *p*-Ph, J = 7.6 Hz), 7.32 (2H, t, *m*-Ph, J = 7.5 Hz), 4.30 (1H, t, H-2, J = 7.9 Hz), 3.64 (3H, s, OMe), 2.17 (1H, m, H-5), 2.05 (2H, m, H-3, H-3′), 1.90 (2H, m, H-4, H-5′), 1.62 (1H, m, H-4′); ^{13}C NMR, δ: 173.2 (C═O), 137.9 (*ipso*-Ph), 128.8–129.4 (Ph), 67.6 (C-2), 60.3 (C-1), 52.3 (OMe), 33.4 (C-5), 30.2 (C-3), 20.4 (C-4).

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