IODINE/TOLUENESULFONIC ACID: A NOVEL CATALYST FOR ISOPROPYLIDENATION IN CARBOHYDRATE CHEMISTRY

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Received December 15, 2006
Accepted April 29, 2007

A novel catalyst for *O*-isopropylidenation of carbohydrates, a mixture of toluenesulfonic acid and iodine, was developed.

Keywords: Iodine; Toluenesulfonic acid; Isopropylidene; Carbohydrates; Synthesis; Protecting group.

Carbohydrates and their derivatives play an important role in biological processes in animals and plants, and have found wide applications in pharmaceuticals and related fields. The isopropylidene group is a considerably important protective group in the synthesis of a variety of carbohydrate derivatives[1–3].

A number of isopropylidenation reagents have been developed so far, among which $MeC(OMe)=CH_2$ (ref.[4]), $Me_2C(OMe)_2$ (ref.[5]), and acetone[6,7] are major ones. However, the first two, derivatives of acetone, are more expensive than acetone itself and unsatisfactory in many cases. The classical method of introduction of isopropylidene functionality is the reaction of the substrate with acetone in the presence of an acid catalyst. Here, we would like to report on a novel catalyst of the reaction, a mixture of iodine and toluenesulfonic acid.

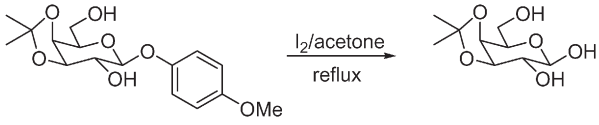
In the total synthesis of a cytotoxic natural product 4″-*O*-acetylmananthoside B[8], compound **2** was required, which could be obtained by isopropylidenation of glycoside **1** (Scheme 1).

1 2

SCHEME 1

doi:10.1135/cccc20071214

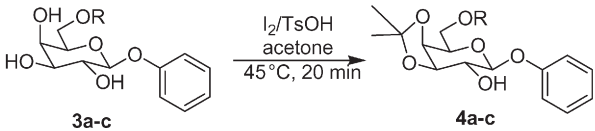
At first we employed the classical reagents, acetone/toluenesulfonic acid and acetone/concentrated sulfuric acid, for isopropylidenation; however, both the reactions involving the two reagents were sluggish, a certain amount of the substrate remained unreacted, and several impurities were also formed, complicating the work-up. We then turned to the reagent[6] acetone/I_2, which was shown to work well only on small scales (less than 0.2 g). When the reaction was scaled up to 1 g or more, the reaction became unreliable, and it did not occur at all at room or slightly elevated temperature (below reflux) even after 12 h stirring. Reflux was subsequently employed to accelerate the reaction; however, the reaction proceeded to completion in an unpredictable period, ranging from several seconds to one hour, and the product **2** was rapidly oxidatively cleaved (Scheme 2). After accumulation of experience with this reagent, a facile and reliable catalyst was devised, a mixture of iodine and toluenesulfonic acid, which is capable of catalyzing isopropylidenation of **1** with acetone. Thus, the isopropylidenation of **1** with acetone in the presence of iodine and toluenesulfonic acid as catalyst proceeded smoothly within 20 min at 45 °C. The reaction is rather clean and could be scaled up to several grams.



2

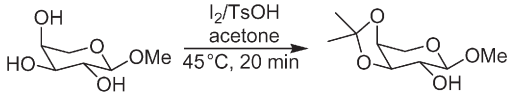
SCHEME 2

Encouraged by the outstanding power of this catalyst, the application of this catalyst to other substrates in carbohydrate chemistry was attempted (Scheme 3). Under almost the same reaction conditions, three carbohydrate substrates were readily isopropylidenated; the reactions were clean and no impurities were detected.



3a-c **4a-c**

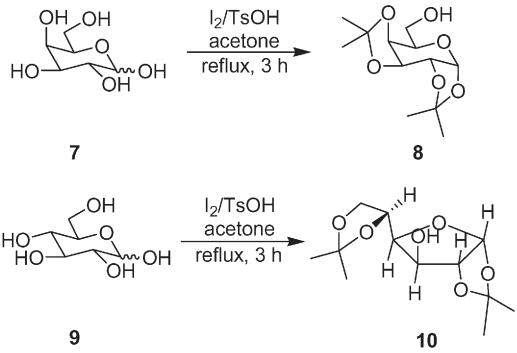
3a, **4a**, R = H; **3b**, **4b**, R = $OCC(CH_3)_3$; **3c**, **4c**, R = Bz



5 **6**

SCHEME 3

Application of this catalyst to simple monosaccharides was further carried out, the results being also satisfactory (Scheme 4). However, it should be noted that isopropylidenation of simple monosaccharides such as D-galactose (**7**) and D-glucose (**9**) required more vigorous conditions than that mentioned above. Thus, **7** and **9** were isopropylidenated with acetone in the presence of iodine/toluenesulfonic acid at reflux in 3 h, whereas methyl β-L-arabinopyranoside (**5**) was readily converted to isopropylidene derivative **6** under milder conditions.



SCHEME 4

The advantage of the iodine/toluenesulfonic acid catalyst over iodine alone may be attributable to the addition of toluenesulfonic acid. The acid appeared to improve the solubility of the substrate in acetone and activate iodine. Only a suspension of reagents forms if the substrate and iodine in acetone were stirred even after a long period and no reaction occurred in most cases or the reaction was initiated by an unknown factor in an unpredictable period of time. However, when toluenesulfonic acid was added, the suspension dissolved at a reasonable rate and the reaction proceeded smoothly and predictably. Thus, a preliminary conclusion can be drawn that if the substrates to be isopropylidenated are soluble or slightly soluble in acetone (**1**, **2**, **3a**–**3c** and **5**), then the reaction can smoothly proceed to completeness (45 °C, 20 min). If the substrates are little soluble in acetone (**7** and **9**), vigorous conditions (reflux, 3 h) are necessary to improve the solubility and ensure an acceptable reaction rate.

EXPERIMENTAL

The melting points were measured with an XT-4 microscopic apparatus and are uncorrected. The ^{1}H NMR spectra were recorded with a Bruker AV 300 or a Bruker AV 600 spectrometer, with $CDCl_3$, methanol-d_4 or DMSO-d_6 as solvent and TMS as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. The IR spectra (wavenumbers

in cm^{-1}) were measured on a Thermo Nicolet Avatar 370 FT spectrophotometer in KBr pellets. The mass spectra were obtained on an ABI MAT-212 apparatus using electrospray ionization (ESI) technique. The elemental analyses were carried out with an Elementar EI Vario III CHN analyzer. Specific rotations were measured with a WZZ-2A automatic polarimeter under standard conditions.

A Typical Procedure of Isopropylidenation of Carbohydrates **1**, **3a**–**3c** and **5**

A 100-ml round-bottomed flask was charged with substrate (1.0 g), iodine (20 mg) and acetone (15 ml). The resulting mixture was stirred at 45 °C to form a suspension, into which toluenesulfonic acid monohydrate (20 mg) was added in one portion. Stirring was continued for another 20 min until the initially insoluble mass dissolved and TLC showed a complete conversion.

On cooling, the mixture could be directly subjected to column chromatography. Alternatively, the mixture was diluted with dichloromethane (50 ml), washed successively with saturated aqueous sodium hydrogencarbonate, 5% aqueous sodium sulfite and brine, and dried over anhydrous sodium sulfate. The organic phase was evaporated on a rotary evaporator to give the crude product, which was chromatographed on silica gel with ethyl acetate and petroleum ether as eluents.

4-Methoxyphenyl 3,4-O-isopropylidene-β-D-galactopyranoside (**2**), yield 88%, m.p. 139–139.5 °C; ref.[9] gives m.p. 133–134 °C. $[\alpha]_D^{20}$ –30.5 (*c* 1.0, $CHCl_3$). For $C_{16}H_{22}O_7$ (326.3) calculated: 58.89% C, 6.79% H; found: 58.82% C, 6.77% H. IR: 3333 (OH); 3062 (Ar-H); 1509, 1465 (benzene ring); 1384 (Me); 1230, 1080, 1041 (C–O). ^{1}H NMR (300 MHz, DMSO-d_6): 6.95–6.98, 6.83–6.86 dd, 2 H each, *J* = 9.0 (Ar-H); 5.53–5.55 d, 1 H, *J* = 5.1 (OH-2); 4.84–4.87 t, 1 H, *J* = 5.6 (H-4); 4.70–4.73 d, 1 H, *J* = 8.1 (H-1); 4.14–4.17 m, 1 H (H-5); 4.01–4.05 t, 1 H, *J* = 6.2 (H-3); 3.91–3.95 t, 1 H, *J* = 6.2 (H-2); 3.70 s, 3 H (MeO); 3.53–3.58 m, 2 H (H-6); 3.40–3.47 m, 1 H (OH-6); 1.42, 1.27 ss, 3 H each (CMe_2). ^{13}C NMR (75 MHz, DMSO-d_6): 154.52, 151.45, 117.80, 114.57 (Ar C); 108.86 (C-1); 101.22 (quaternary C in CMe_2); 79.39 (C-2); 73.51 (C-3); 73.28 (OMe); 72.32 (C-4); 60.54 (C-5); 55.49 (C-6); 28.32, 26.57 (2 Me in CMe_2). ESI-MS (*m/z*): 344.4 [M + H_2O], 349.3 [M + Na].

Phenyl 3,4-O-isopropylidene-β-D-galactopyranoside (**4a**), yield 92%, m.p. 137.5–140 °C. $[\alpha]_D^{20}$ –33.7 (*c* 1.0, $CHCl_3$). For $C_{15}H_{20}O_6$ (296.3) calculated: 60.80% C, 6.80% H; found: 60.71% C, 6.83% H. IR: 3274 (OH); 3062 (Ar-H); 1601, 1591, 1493 (benzene ring); 1380 (Me); 1236, 1076, 1053 (C–O). ^{1}H NMR (600 MHz, methanol-d_4): 7.28–7.30 m, 2 H (Ar-H); 7.09–7.10 m, 2 H (Ar-H); 7.01–7.02 m, 1 H (Ar-H); 4.85–4.87 d, 1 H, *J* = 8.1 (H-1); 4.28–4.29 d, 1 H, *J* = 5.47 (H-2); 4.13–4.16 t, 1 H, *J* = 6.3 (H-3); 4.04–4.06 m, 1 H (H-5); 3.80–3.81 m, 2 H (H-6); 3.68–3.71 m, 1 H (H-4); 1.37, 1.53 ss, 3 H each (CMe_2). ^{13}C NMR (150 MHz, methanol-d_4): 157.34, 128.73, 121.74, 116.07 (Ar C); 109.45 (C-1); 100.10 (quaternary C in CMe_2); 79.10 (C-2); 73.52 (C-3); 73.31 (C-4); 72.46 (C-5); 60.69 (C-6); 26.75, 24.86 (2 Me in CMe_2). ESI-MS (*m/z*): 314.3 [M + H_2O], 319.3 [M + Na].

Phenyl 3,4-O-isopropylidene-6-O-pivaloyl-β-D-galactopyranoside (**4b**), yield 90%, m.p. 149.5–151 °C. $[\alpha]_D^{20}$ –12.1 (*c* 1.0, $CHCl_3$). For $C_{20}H_{28}O_7$ (380.4) calculated: 63.14% C, 7.42% H; found: 63.05% C, 7.40% H. IR: 3436 (OH); 3060 (Ar-H); 1733 (C=O); 1600, 1587, 1499, 1488 (benzene ring); 1387 (Me); 1227, 1071, 1053 (C–O). ^{1}H NMR (600 MHz, $CDCl_3$): 7.28–7.30 m, 2 H (Ar-H); 7.05–7.08 m, 3 H (Ar-H); 4.78–4.79 d, 1 H, *J* = 8.3 (H-1); 4.42–4.45 m, 1 H (H-3); 4.33–4.37 m, 1 H (H-4); 4.17–4.22 m, 3 H (H-5 and H-6); 3.87–3.89 t, 1 H, *J* = 7.5 (H-2); 1.39, 1.58 ss, 3 H each (CMe_2); 1.23 s, 9 H (CMe_3). ^{13}C NMR (150 MHz, $CDCl_3$): 177.99

(C=O); 156.66, 129.22, 122.79, 116.56 (Ar C); 110.48 (C-1); 100.09 (quaternary C in CMe_2); 78.35 (C-2); 73.01 (C-3); 72.97 (C-4); 71.10 (C-5); 63.04 (C-6); 38.47 ($(CH_3)_3C$); 27.80 ($(CH_3)_3C$); 26.84, 26.01 (2 Me in CMe_2). ESI-MS (*m/z*): 398.6 [M + H_2O], 403.7 [M + Na].

Phenyl 6-O-benzoyl-3,4-O-isopropylidene-β-D-*galactopyranoside* (**4c**), yield 95%, m.p. 141–143 °C. $[\alpha]_D^{20}$ –5.6 (*c* 1.0, $CHCl_3$). For $C_{22}H_{24}O_7$ (400.4) calculated: 65.99% C, 6.04% H; found: 65.92% C, 6.06% H. IR (KBr): 3429 (OH); 3057 (Ar-H); 1725 (C=O); 1599, 1588, 1497 (benzene); 1271, 1114, 1070 (C–O). ^{1}H NMR (600 MHz, $CDCl_3$): 8.07–8.08 m, 2 H (Ar-H of benzoyl); 7.49–7.63 m, 1 H (Ar-H of benzoyl); 7.46–7.49 m, 2 H (Ar-H of benzoyl); 7.18–7.20 m, 2 H (Ar-H of PhO); 7.02–7.06 m, 3 H (Ar-H of PhO); 4.80–4.81 d, 1 H, *J* = 8.2 (H-1); 4.72–4.77 m, 1 H (H-2); 4.58–4.62 m, 1 H (H-4); 4.30–4.32 m, 2 H (H-6); 4.24–4.26 m, 1 H (H-5); 3.91–3.94 t, 1 H, *J* = 7.7 (H-2); 1.42, 1.61 ss, 3 H each (CMe_2). ^{13}C NMR (150 MHz, $CDCl_3$): 166.00 (C=O); 156.61, 132.99, 129.47, 129.43 (C in benzoyl); 129.17, 128.17, 122.74, 116.59 (C in phenyl); 110.65 (C-1); 100.10 (quaternary C in CMe_2); 78.48 (C-2); 73.07 (C-3); 73.03 (C-4); 71.25 (C-5); 63.39 (C-6); 27.81, 26.06 (2 Me in CMe_2). ESI-MS (*m/z*): 418.7 [M + H_2O], 423.6 [M + Na].

Methyl 3,4-O-isopropylidene-β-L-*arabinopyranoside* (**6**), yield 87%. $[\alpha]_D^{20}$ +199.5 (*c* 1.0, $CHCl_3$); ref.[10] gives $[\alpha]_D^{20}$ +199.1 (*c* 1.0, $CHCl_3$).

A Typical Procedure for Isopropylidenation of Carbohydrates **7** and **9**

Into a 100-ml round-bottomed flask substrate (1.0 g), iodine (60 mg), toluenesulfonic acid monohydrate (50 mg) and acetone (60 ml) were added. The mixture was subsequently refluxed for 3 h until a clear solution formed. On cooling, most acetone was evaporated and the same work-up procedure as above gave the desired products.

1,2:3,4-O-Diisopropylidene-α-D-*galactopyranose* (**8**), yield 77%, colorless oil. $[\alpha]_D^{20}$ –54.1 (*c* 1.0, $CHCl_3$); ref.[7] gives $[\alpha]_D^{20}$ –54.5 (*c* 1.0, $CHCl_3$).

1,2:5,6-O-Diisopropylidene-α-D-*glucofuranose* (**10**), yield 73%, m.p. 109.5–111 °C; ref.[7] gives m.p. 110 °C.

Financial support from the Natural Science Foundation of Shandong Province (Z2004c06) is gratefully acknowledged.

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