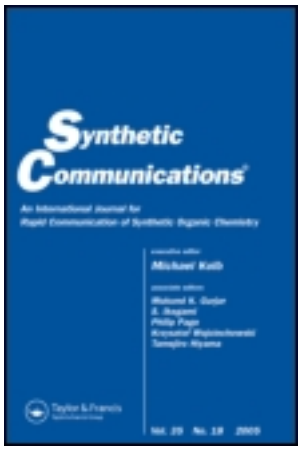

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NOVEL PREPARATION OF (2-AZIDOMETHYL)BENZOIC ACID AND AN APPLICATION AS A PROTECTIVE GROUP

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ABSTRACT

A novel preparation method of 2-(azidomethyl)benzoic acid, a precursor of (2-azidomethyl)benzoyl (AZMB) protective group, was developed which can provide pure sample in gram scale without chromatographic purifications. Reductive cleavage using triphenylphosphine was found to be effective in the case of sterically hindered ester that resists under basic hydrolysis.

Key Words: (2-Azidomethyl)benzoate; Hydroxyl protective group; Selective cleavage

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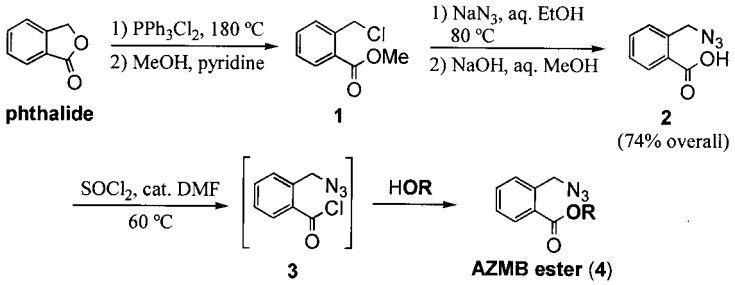
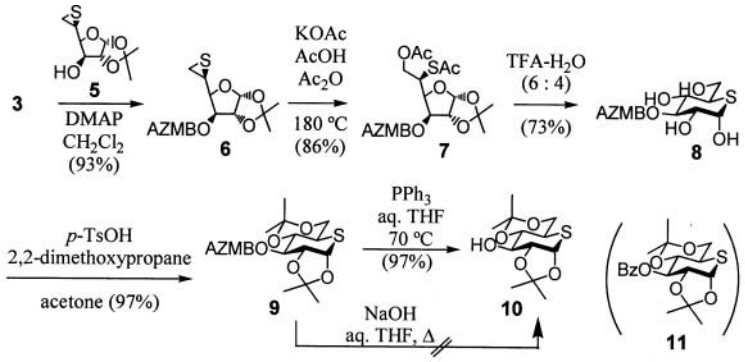
In the syntheses of polyhydroxylated molecules, protective groups of alcohol functions play key roles and variety of those which can be introduced and removed under mild conditions distinguishing with other ones have been developed.[1] Recentry, Sekine and his co-workers have developed a novel benzoyl derivative (2-azidomethyl)benzoyl (AZMB) ester **4**, cleavable by a reduction ($MePPh_2$, $NaBH_3CN$, $Pd/C\text{-}H_2$) of the azido group which results a formation of phtalamide, and they have also demonstrated the effectiveness of **4** in synthesis of nucleosides.[2] Now, we would like to report an alternative preparation of (2-azidomethyl)benzoic acid (**2**), a precursor of **4**, as well as our findings in its applications.

Heating phthalide with dichlorotriphenylphosphorane at 180°C without solvent[3] and following treatment of the crude product with methanol in the presence of pyridine gave methyl ester **1** (Sch. 1). Without purification, **1** was treated with sodium azide in aqueous ethanol to take place a replacement of the chlorine with azido group. Then, methyl ester was hydrolyzed by aqueous sodium hydroxide and the crude product was recrystallized from hot hexane to provide pure **2** as needles (m.p. = 78.0–79.0°C, lit 73–75°C[2]) in 74% yield overall. It was found that **2** is stable enough to store for several months in refrigerator. Sekine et al. disclosed an efficient procedure of AZMB group,[2] however, this method also provide it readily in gram scale. For protection of alcohols, **2** was converted into the corresponding acid chloride **3**, before use, by excess thionyl chloride at 60°C and catalytic amount of *N*,*N*-dimethylformamide. The crude **3** was subjected to alcohol protection after removal of the volatile materials under reduced pressure.

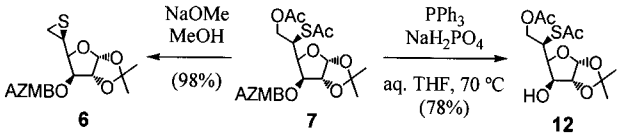
We applied AZMB group to a preparation of 3-free thioglucopyranose derivative **10** (Sch. 2). The crude **3** was treated with alcohol **5**[4] in the presence of *N*,*N*-dimethyl-4-aminopyridine to produce AZMB ester **6** in 93% yield. The reaction was very slow when pyridine was employed instead of DMAP. Acetolysis of **6** was performed by heating at 140°C in a mixture



Scheme 1.



Scheme 2.



Scheme 3.

of potassium acetate, acetic acid, and acetic anhydride to give **7** in 86% yield. The azido group was not affected under those harsh conditions. AZMB group was also found to be quite stable under acidic conditions that treatment of **7** with 60% aqueous trifluoroacetic acid solution for 2 days took place removals of the acetonide, *S*-acetyl, *O*-acetyl groups, and succeeding rearrangement from the furanose to a thiopyranose ring to afford **8** in 73% yield. Migration or cleavage of AZMB group was not observed during the reaction. After transformation into bisacetonide **9**, deprotection of AZMB group was attempted. It was found that AZMB group did not react at all when hydrolysis was performed with sodium hydroxide in aqueous tetrahydrofuran (THF) at 70°C. However, when it was performed with triphenylphosphine in aqueous THF the cleavage of the AZMB proceeded smoothly to afford **10** in quantitative yield. Interestingly, benzoate analogue **11**, which could be prepared in the similar manner to that of **9**, was hydrolyzed by aqueous NaOH even it took 10 h. Thus, it can be concluded that AZMB group can be more stable than benzoate derivative under aqueous basic conditions.

Availability of AZMB group could also be demonstrated employing **7**. Treatment of **7** with triphenylphosphine in the presence of sodium dihydrogenphosphate in aqueous THF at 70°C for 1 h resulted a selective cleavage

of AZMB group smoothly to afford alcohol **12** in 78% yield (Sch. 3).[5] When the reaction was performed without phosphate, the yield of **12** was decreased (<50%) due to undesired by-products. Interestingly, basic methanolysis of **7** employing two equivalents of sodium methoxide gave thiirane **5** in 98% yield.[6]

Utilizing this protective group, synthesis of oligo-thiosaccharide which may prevent using benzyl group due to sulfide function is now under progress in our laboratory.

EXPERIMENTAL

2-Azidomethylbenzoic Acid (2)

A mixture of phthalide (5.30 g, 39.0 mmol) and Ph_3PCl_2 (15 g, 45 mmol) was heated at 180°C for 2 h under Ar atmosphere. Upon heating, the solid reaction mixture changed to an orange solution. After cooling to 0°C, methanol (10 mL) and pyridine (10 mL) were added successively into the mixture and the whole mixture was stirred for 1 h. Hexane (200 mL) and H_2O (100 mL) were added to the mixture. The precipitate was removed by filtration and the aqueous layer was removed. The organic layer was washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to provide methyl 2-chloromethylbenzoate (**1**) in an almost pure state. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.93 (3H, s), 5.05 (2H, s), 7.39 (1H, ddd, $J = 1.6$, 6.8, 8.5 Hz), 7.54 (2H, m), 7.97 (1H, dd, $J = 1.6$, 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 44.4, 52.2, 128.4, 129.0, 130.8, 131.1, 132.5, 138.7, 167.0. The crude **1** was dissolved in ethanol (50 mL) and H_2O (25 mL) and it was stirred with sodium azide (6.0 g, 92.3 mmol) at 60°C for 2 h. After the mixture was concentrated under reduced pressure until the whole volume became a third, the resulting mixture was extracted with hexane (50 mL × 3), combined, and concentrated in vacuo to give a residue which was diluted with methanol (50 mL) and aqueous sodium hydroxide solution (3.0 g in 20 mL of H_2O). After stirring vigorously for 3 h, the mixture was concentrated until the whole volume became a third. The residual mixture was washed with ether (20 mL) and then aqueous solution was acidified by addition of 12 M aqueous HCl solution (5.0 mL) to give an emersion. After extraction with AcOEt (50 mL × 3), the combined organic solutions were washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to give white solid. Recrystallization from hexane afforded pure **2** as white needles. M.p. = 78.0–79.0°C (lit. 73–75°C[2]). The IR and NMR data were identical with these of reported by Sekine et al.[2]

2-Azidomethylbenzoyl Chloride (3)

A mixture of **2** and catalytic amount of *N*,*N*-dimethylformamide in thionly chloride (excess) was heated at 60°C for 2 h. After cooling to room temperature, toluene was added, and substances volatile were removed azeotropically by rotary evaporator and then those were removed thoroughly using vacuum pump for 30 min to give a crude acid chloride **3** [^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.75 (2H, s), 7.53 (1H, t, $J = 7.2$ Hz), 7.60 (1H, d, $J = 7.2$ Hz), 7.67 (1H, t, $J = 7.46$ Hz), 8.32 (1H, d, $J = 7.2$ Hz)] which was directly used for the esterification.

AZMB Ester 6

The acid chloride **3**, prepared by the above procedure employing 85 mg of **2** (480 μmol), thionyl chloride (1.0 mL), and *N*,*N*-dimethylformamide (3.0 μL), was stirred with alcohol **5** (134 mg, 615 μmol) and 4-(*N*,*N*-dimethylamino)pyridine (117 mg, 959 μmol) in CH_2Cl_2 (2.0 mL) at 0°C for 2 h. The mixture was poured into water and extracted with ether (30 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Silica gel column chromatography eluted with AcOEt : hexane (15 : 85) gave **6** (215 mg, 570 μmol, 93%) as an oil $[\alpha]_D^{26}$ -52.4° (*c* 11.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.34, 1.52 (each, 3H, s), 2.44 (1H, dd, $J = 1.4$, 4.9 Hz), 2.62 (1H, dd, $J = 1.4$, 6.3 Hz), 3.07 (1H, ddd, $J = 4.9$, 6.3, 8.8 Hz), 3.82 (1H, dd, $J = 2.9$, 8.8 Hz), 4.70 (1H, d, $J = 3.9$ Hz), 4.80, 4.88 (each 1H, d, $J = 14.6$ Hz), 5.49 (1H, d, $J = 2.9$ Hz), 6.02 (1H, d, $J = 3.9$ Hz), 7.43 (1H, dt, $J = 1.0$, 7.5 Hz), 7.53 (1H, brd, $J = 7.5$ Hz), 7.59 (1h, dt, $J = 1.0$, 7.5 Hz), 8.03 (1H, dd, $J = 1.0$, 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 24.8, 26.2, 26.7, 29.0, 53.0, 78.2, 83.2, 85.0, 105.5, 112.5, 127.8, 128.3, 130.0, 131.1, 133.4, 137.9, 165.2. IR (film, cm^{-1}) 2100, 1720, 1250, 1080, 1020. EI-MS (%, rel int.) 362 ($(M - CH_3)^+$, 7), 291 (4), 132 (100), HIMS Calcd. for $C_{16}H_{16}N_3O_5S$ [$(M - CH_3)^+$]: 362.0811. Found: $m/z = 362.0830$.

Thioacetate 7

A suspension of **6** (316 mg, 838 μmol) and potassium acetate (400 mg, 4.12 mmol) in a mixture of acetic acid (1.0 mL) and acetic anhydride (10 mL) was stirred at 140°C for 14 h. After cooling to room temperature, the solvent was removed by rotary evaporator. The residue was suspended with H_2O (50 mL) and it was extracted with AcOEt (30 mL × 3). The combined

organic layer was washed with brine anhydrous $MgSO_4$, and concentrated in vacuo. Silica gel column chromatography of the residue with AcOEt : hexane (20 : 80) gave **7** (345 mg, 720 μmol, 86%) as fine needles (from AcOEt–hexane). M.p. = 108–109°C. $[\alpha]_D^{26}$ −50.8° (*c* 7.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.33, 1.55, 2.06, 2.20 (each 3H, s), 4.17 (1H, ddd, J = 2.9, 4.9, 10.7 Hz), 4.39 (1H, dd, J = 4.9, 11.7 Hz), 4.47 (1H, dd, J = 2.9, 11.7 Hz), 4.54 (1H, dd, J = 2.9, 10.7 Hz), 4.60 (1H, d, J = 3.4 Hz), 4.79 (2H, s), 5.49 (1H, d, J = 2.9 Hz), 5.98 (1H, d, J = 3.4 Hz), 7.43 (1H, dt, J = 1.0, 7.5 Hz), 7.50 (1H, brd, J = 7.5 Hz), 7.59 (1H, dt, J = 1.4, 7.5 Hz), 8.03 (1H, dd, J = 1.4, 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 20.7, 26.3, 26.7, 30.5, 76.4, 77.3, 83.0, 105.1, 112.5, 127.5, 128.3, 128.4, 130.0, 131.5, 133.4, 137.7, 165.1, 170.5, 192.6. IR (KBr, cm^{-1}) 2110, 1740, 1715, 1700, 1250, 1240, 1080. EI-MS (%, rel int.) 464 ($(M-CH_3)^+$, 5), 408 (8), 132 (86), 43 (100), HIMS Calcd. for $C_{20}H_{22}N_3O_8S$ [$(M-CH_3)^+$]: 464.1128. Found: m/z = 464.1118.

α-3-*O*-AZMB-5-Thioglucopyranose (8)

A solution of **7** (230 mg, 480 μmol) in aqueous 60% trifluoroacetic acid (25 mL) was stirred at room temperature for 2 days. The solvent was evaporate in vacuo and the residue was purified by silica gel column chromatography eluted with acetone : CH_2Cl_2 (30 : 70) gave **8** (124 mg, 349 μmol, 73%) as an oil. $[\alpha]_D^{26}$ +96.0° (*c* 12.3, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD, ppm) δ 3.51 (1H, ddd, J = 4.0, 4.8, 9.2 Hz). 3.83 (1H, dd, J = 9.2, 10.8 Hz), 3.90 (3H, m), 4.79 (2H, s), 4.93 (1H, d, J = 3.6 Hz), 7.44 (1H, d, J = 1.5, 8.0 Hz), 7.52 (1H, brd, J = 8.0 Hz), 7.58 (1H, dt, J = 1.5, 8.0 Hz), 8.04 (1H, dd, J = 1.5, 8.0 Hz). ^{13}C NMR (100 MHz, CD_3OD, ppm) δ 45.0, 53.7, 62.0, 74.3, 75.1, 76.2, 78.5, 129.1, 130.8, 131.6, 131.9, 133.4, 138.1, 168.4. IR (film, cm^{-1}) 3375, 2100, 1710, 1265, 1140, 1090, 1050. FAB-MS (%, rel int.) 354 ($(M-H)^-$, 9), 101 (100), 42 (41), HIMS Calcd. for $C_{14}H_{16}N_3O_6S$ [$(M-H)^-$]: 354.0760. Found: m/z = 354.0778.

α-3-*O*-AZMB-1,2-4,5-Diisopropylidene-5-thioglucopyranose (9)

A solution of **8** (32.0 mg, 94.3 μmol) in a mixture of 2,2-dimethoxypropane (1.0 mL) and acetone (1.0 mL) was stirred with *p*-toluenesulfonic acid monohydrate (1.9 mg, 10 μmol) at room temperature for 3 h. After neutralization by the addition of triethylamine (5 μL), the solvent was removed under reduced pressure. Silica gel column chromatography of

the residue with acetone : CH_2Cl_2 (10 : 90) gave **9** (38.3 mg, 91.4 μmol, 97%) as an oil. $[\alpha]_D^{26} + 74.0^\circ$ (*c* 11.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.36, 1.41, 1.47, 1.67 (each 3H, s), 3.38 (1H, dt, $J = 5.2$, 11.2 Hz), 3.74 (1H, t, $J = 11.2$ Hz), 3.89 (1H, dd, $J = 5.2$, 11.2 Hz), 3.99 (1H, t, $J = 10.0$ Hz), 4.34 (1H, dd, $J = 5.2$, 8.4 Hz), 4.71, 4.79 (each 1H, d, $J = 14.4$ Hz), 5.16 (1H, d, $J = 5.2$ Hz), 5.35 (1H, dd, $J = 8.4$, 10.0 Hz), 7.41 (1H, dt, $J = 1.6$, 8.0 Hz), 7.50 (1H, brd, $J = 8.0$ Hz), 7.56 (1H, dt, $J = 1.6$, 8.0 Hz), 7.95 (1H, dd, $J = 1.6$, 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 18.8, 26.7, 27.8, 29.2, 36.4, 52.6, 61.4, 72.7, 74.7, 76.4, 78.4, 99.4, 110.4, 128.0, 129.6, 129.7, 130.7, 132.4, 136.7, 166.0. IR (film, cm^{-1}) 2100, 1725, 1255, 1215, 1190, 1080, 1050, 1030. EI-MS (%, rel int.) 420 ($(M - CH_3)^+$, 9), 318 (12), 258 (10), 200 (12), 132 (100), HIMS Calcd. for $C_{19}H_{22}N_3O_6S$ [$(M - CH_3)^+$]: 420.1229. Found: $m/z = 420.1212$.

α-1,2-4,5-Diisopropylidene-5-thioglucopyranose (10)

A solution of **9** (48.0 mg, 110 μmol) in a mixture of THF (1.0 mL) and H_2O (0.5 mL) was heated at 70°C with triphenylphosphine (34.6 mg 132 μmol) for 2 h. The reaction completed within 1 h by monitored with silica gel TLC. The mixture was concentrated in vacuo to give a residue. Silica gel column chromatography of the residue with AcOEt : hexane (25 : 75) gave **10** (29.3 mg, 106 μmol, 97%) as a prism. M.p. = 99–100°C (from hexane). $[\alpha]_D^{26} + 174.2^\circ$ (*c* 8.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.41, 1.44, 1.51, 1.58 (each 3H, s), 2.79 (1H, br), 3.17 (1H, dt, $J = 5.4$, 10.8 Hz), 3.65 (1H, dd, $J = 7.8$, 9.7 Hz), 3.62 (2H, m), 3.84 (1H, dd, $J = 11.7$ Hz), 4.15 (1H, dd, $J = 4.8$, 7.3 Hz), 5.10 (1H, d, $J = 4.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 19.1, 26.6, 28.3, 29.4, 61.4, 74.1, 74.3, 75.9, 80.1, 99.7, 109.9. IR (KBr, cm^{-1}) 3475, 1380, 1220, 1160, 1050, 1015, 865. EI-MS (%, rel int.) 276 (M^+, 4), 261 ($(M - CH_3)^+$, 16), 218 (34), 59 (100), 43 (72), HIMS Calcd. for $C_{12}H_{20}O_5S$ [$(M - CH_3)^+$]: 276.1031. Found: $m/z = 276.1017$.

Treatment of 7 with NaOMe

A solution of **7** (14.0 mg, 29.2 μmol) and sodium methoxide (3.0 mg, 55.5 μmol) in a mixture of methanol (1.0 mL) and THF (0.4 mL) was stirred at room temperature. After stirring for 10 h, the mixture was poured into brine (50 mL) and it was extracted with Et_2O (30 mL × 3). The combined organic layer was dried with anhydrous $MgSO_4$, and concentrated in vacuo. Silica gel column chromatography of the residue with AcOEt : hexane

(20 : 80) gave **6** (10.8 mg, 28.6 μmol, 98%), ^{1}H NMR data of the sample was identical with that of AZMB ester thiirane **6**.

Treatment of 7 with PPh_3

A mixture of **7** (10.1 mg, 21.1 μmol), sodium dihydrogenphosphate dihydrate (8.6 mg, 55.1 μmol), and triphenylphosphine (8.0 mg, 30.5 μmol) in a mixture of THF (1.0 mL) and H_2O (0.3 mL) was heated at 70°C for 1 h. The mixture was poured into water (20 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic solution was washed with saturated sodium chloride solution (20 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. Silicagel column chromatography of the residue with AcOEt : hexane (35 : 65) gave **12** as amolphous powder (5.3 mg, 16.6 μmol, 78%).[8] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.25, 1.50, 2.07, 2.41 (each 3H, s), 3.96 (1H, ddd, $J = 3.9$, 4.9, 10.7 Hz), 4.10 (1H, d, $J = 1.9$ Hz), 4.18 (1H, dd, $J = 1.9$, 10.7 Hz), 4.45 (1H, dd, $J = 4.9$, 11.7 Hz), 4.47 (1H, dd, $J = 3.9$, 11.7 Hz), 4.53 (1H, d, $J = 3.4$ Hz), 5.92 (1H, d, $J = 3.4$ Hz). The structure of **12** was confirmed by converting the sample into reported acetate[7] as follows. A solution of **12** (3.0 mg, 9.38 μmol) in a mixture of acetic anhydride (100 μL) and pyridine (1.0 mL) at room temperature for 12 h. After concentration in vacuo, the residue was purified employing silica gel column chromatography. Elution with AcOEt : hexane (15 : 85) gave the corresponding acetate (3.1 mg, 8.56 μmol, 91%). M.p. = 151°C (from hexane, lit. 152–154°C[7]). The ^{1}H NMR spectrum of this sample was identical with that of reported, prepared by following their procedure.

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