Selective Benzoylation of Diols with 1-(Benzoyloxy)benzotriazole

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Selective benzoylation of diols is one of the most useful reactions in the selective protection of hydroxy groups in organic synthesis. A number of methods have been developed for the selective benzoylation of diols involving various reagents such as benzoyl cyanide,[1] benzoylimidazole,[2] and benzoyltetrazole.[3,4] In general, regioselectivity in benzoylation of diols with reported methods is not always great.

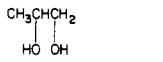
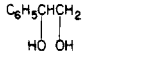
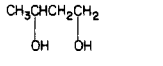
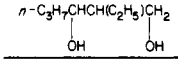
We have found that the use of 1-(benzoyloxy)benzotriazole[5] is very effective in the selective benzoylation of diols under mild conditions. 1-(Benzoyloxy)benzotriazole was conveniently prepared in 85% yield by the reaction of benzoyl chloride with equimolar amounts of 1-hydroxybenzotriazole and triethylamine in methylene chloride at room temperature for 20 min.

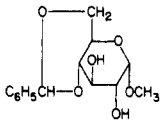
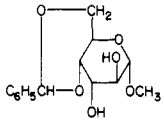
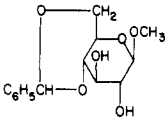
First, we have studied selective benzoylation of simple diols having primary and secondary hydroxy groups such as 1,2-propanediol, phenylethanediol, and 1,3-butanediol. Reaction of 1,2-propanediol with equimolar amounts of 1-(benzoyloxy)benzotriazole and triethylamine in methylene chloride at room temperature in 24 h gave 89% of the monobenzoate along with 4% of the dibenzoate. The monobenzoate turned out to be a 92:8 mixture of the primary benzoate and the secondary benzoate, which was determined by NMR analysis. Similar results were obtained with phenylethanediol as shown in Table I. Better selectivity was observed in the benzoylation of 1,3-diols. Reaction of 1,3-butanediol with equimolar amounts of the reagent and triethylamine at room temperature in 24 h gave 93% of the primary monobenzoate along with a small amount of the dibenzoate, whereas benzoylation of 2-ethyl-1,3-hexanediol gave almost exclusively the primary monobenzoate under the same conditions.

In view of the great importance of the selective protection of hydroxy groups in carbohydrate chemistry,[6,7] we have studied selective benzoylation with several carbohydrate derivatives. Reaction of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with equimolar amounts of 1-(benzoyloxy)benzotriazole and triethylamine in methylene chloride at room temperature for 5 h afforded a 90:4 mixture of the 2-*O*-benzoate and the 3-*O*-benzoate along with 2% of the 2,3-di-*O*-benzoate. Even better selectivity was achieved with methyl 4,6-*O*-benzylidene-α-D-altropyranoside. Benzoylation occurred exclusively at the 2-hydroxy group, and methyl 4,6-*O*-benzylidene-2-*O*-benzoyl-α-D-altropyranoside was isolated in 90% yield. The selectivity achieved with 1-(benzoyloxy)benzotriazole in the benzoylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside and methyl 4,6-*O*-benzylidene-α-D-altropyranoside is superior to previously reported reagents in terms of the selectivity and the yield. However, selective benzoylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside was much less selective than that of the corresponding α-D-glucoside derivative. Since methyl 4,6-*O*-benzylidene-β-D-glucopyranoside was insoluble in methylene chloride, the reaction was carried out in tetrahydrofuran and gave a 50:43 mixture of the 2-*O*-benzoate and the 3-*O*-benzoate without the formation of the 2,3-di-*O*-benzoate.

Although there are several methods available for selective benzoylation of diols, we believe that the present method offers considerable advantages in terms of high selectivity, high yield, and very mild condition.

Table I. Selective Benzoylation of Diols with 1-(Benzoyloxy)benzotriazole in CH_2Cl_2 at Room Temperature

diol	time, h	product (isolated yield, %) primary benzoate	secondary benzoate	dibenzoate
	24	92[a]	8[a]	(4)
	24	(83)	(9)	(5)
	24	(93)	0	(3)
	24	(95)	0	(<1)

diol	time, h	product (isolated yield, %) 2-*O*-benzoate	3-*O*-benzoate	2,3-di-*O*-benzoate
	5	(90)	(4)	(2)
	72	(90)	0	0
	72[b]	(50)	(43)	0

[a] The ratio was determined by NMR analysis and the monobenzoate was isolated in 89% yield. [b] The reaction was carried out in tetrahydrofuran.

Experimental Section

NMR spectra were recorded with a Varian FT-80A spectrometer and IR spectra were obtained on a Perkin-Elmer 267 spectrometer. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Optical rotations were recorded on an Autopol III automatic polarimeter. Analytical thin-layer chromatography was performed on precoated silica gel glass plates (0.25 mm, 60F-254, E. Merck) and silica gel (silica gel 60, E. Merck, 0.063-0.200 mm) was used for column chromatography.

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The products obtained were known products in all cases. Identification was effected through alternate preparation by known procedures. Since the reactions studied here are all similar in many respects, typical reactions will be described as specific examples.

Preparation of 1-(Benzoyloxy)benzotriazole. To a stirred solution of 1-hydroxybenzotriazole (675 mg, 5 mmol) and triethylamine (770 μL, 5.5 mmol) in methylene chloride (4 mL) at room temperature was slowly added benzoyl chloride (580 μL, 5 mmol). The reaction mixture was stirred at room temperature for 20 min, diluted with methylene chloride (40 mL), washed with saturated $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and evaporated to dryness. The crude product was recrystallized from methylene chloride and petroleum ether to afford 1-(benzoyloxy)benzotriazole (1.02 g) in 85% yield: mp 77–79 °C [lit.[5a] mp 77–79 °C, lit.[5b] 80–81 °C]; IR (KBr) 1775 cm^{-1} [lit.[5b] 1770 cm^{-1}].

Selective Benzoylation of 1-Phenyl-1,2-ethanediol. To a stirred solution of 1-phenyl-1,2-ethanediol (280 mg, 2.0 mmol) and 1-(benzoyloxy)benzotriazole (503 mg, 2.1 mmol) in methylene chloride (8 mL) at room temperature was added triethylamine (305 μL, 2.2 mmol). The reaction mixture was stirred at room temperature for 24 h, diluted with methylene chloride (30 mL), washed with saturated $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and evaporated to dryness. The crude product was subjected to silica gel column chromatography using hexane and ethyl acetate (6:1) as an eluant to afford the dibenzoate (34 mg, 5%), the primary monobenzoate (390 mg, 83%), and the secondary monobenzoate (42 mg, 9%). The dibenzoate: mp 91–93 °C; NMR ($CDCl_3$) δ 4.55–4.80 (m, 2 H), 6.35 (t, J = 6 Hz, 1 H), 7.15–8.15 (m, 15 H). The primary monobenzoate: mp 65–66 °C; NMR ($CDCl_3$) δ 3.20 (br s, 1 H), 4.35–4.65 (m, 2 H), 5.15 (dd, J = 4, 6 Hz, 1 H), 7.20–7.60 (m, 8 H), 7.90–8.30 (m, 2 H). The secondary monobenzoate: NMR ($CDCl_3$) δ 2.20 (br s, 1 H), 3.90–4.15 (m, 2 H), 6.05 (q, J = 5 Hz, 1 H), 7.20–7.65 (m, 8 H), 7.95–8.30 (m, 2 H).

Selective Benzoylation of Methyl 4,6-*O*-Benzylidene-α-D-glucopyranoside. To a stirred solution of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (565 mg, 2.0 mmol) and 1-(benzoyloxy)benzotriazole (485 mg, 2.0 mmol) in methylene chloride (8 mL) at room temperature was added triethylamine (300 μL, 2.2 mmol). The reaction mixture was stirred at room temperature for 5 h, diluted with methylene chloride (40 mL), washed with saturated $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and evaporated to dryness. The crude product was subjected to silica gel column chromatography. Elution with hexane and ethyl acetate (6:1) gave the 2,3-di-*O*-benzoate (19 mg, 2%). After the 2,3-di-*O*-benzoate was isolated, elution with hexane and ethyl acetate (3:1) gave the 2-*O*-benzoate (693 mg, 90%), and elution with hexane and ethyl acetate (1:1) gave the 3-*O*-benzoate (29 mg, 4%). Methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzoyl-α-D-glucopyranoside: mp 154 °C [lit.[7a] 154 °C]; $[\alpha]^{25}_D$ +92.2° (0.7, $CHCl_3$) [lit.[7a] $[\alpha]^{26}_D$ +94 ± 2° (1.51, $CHCl_3$)]. Methyl 4,6-*O*-benzylidene-2-*O*-benzoyl-α-D-glucopyranoside: mp 169–170 °C [lit. mp 169–170 °C,[7a] 168–170 °C[7d]; $[\alpha]^{25}_D$ +107.0° (1.3, $CHCl_3$) [lit. $[\alpha]^{26}_D$ +111 ± 2° (1.64, $CHCl_3$)[7a], $[\alpha]_D$ +108° (1, $CHCl_3$)[7d]]. Methyl 4,6-*O*-benzylidene-3-*O*-benzoyl-α-D-glucopyranoside: mp 217–220 °C [lit. mp 219–220 °C,[7a] 218–220 °C[7e]; $[\alpha]^{25}_D$ +33.8° (0.7, $CHCl_3$) [lit. $[\alpha]^{26}_D$ +34.1° (1.10, $CHCl_3$),[7a] $[\alpha]^{20}_D$ +33° (2, $CHCl_3$)[7e]].

Selective benzoylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside and methyl 4,6-*O*-benzylidene-α-D-altropyranoside was carried out in a similar manner as described above. Methyl 4,6-*O*-benzylidene-2-*O*-benzoyl-β-D-glucopyranoside: mp 198–199 °C [lit. mp 195–196 °C,[7d] 195–197 °C[7e]]; $[\alpha]^{25}_D$ −32.8° (0.6, $CHCl_3$) [lit. $[\alpha]^{20}_D$ −34° (0.5, $CHCl_3$),[7d] $[\alpha]^{20}_D$ −34° (1.5, $CHCl_3$)[7e]]. Methyl 4,6-*O*-benzylidene-3-*O*-benzoyl-β-D-glucopyranoside: mp 180–182 °C [lit. mp 177–178 °C,[7d] 182–183 °C[7f]]; $[\alpha]^{25}_D$ −106.5° (0.2, $CHCl_3$) [lit. $[\alpha]^{20}_D$ −107° (0.5, $CHCl_3$)[7d]]. Methyl 4,6-*O*-benzylidene-2-*O*-benzoyl-α-D-altropyranoside: mp 138–139 °C [lit.[7b] mp 138–139 °C]; $[\alpha]^{25}_D$ −3.9° (1.4, $CHCl_3$) [lit.[7b] $[\alpha]^{19}_D$ −5 ± 1° (1.25, $CHCl_3$)].

Registry No. $CH_3CH(OH)CH_2OH$, 57-55-6; $C_6H_5CH(OH)CH_2OH$, 93-56-1; $CH_3CH(OH)CH_2CH_2OH$, 107-88-0; 1-$C_3H_7CH(OH)CH(C_2H_5)CH_2OH$, 94-96-2; $CH_3CH(OH)CH_2OCOC_6H_5$, 37086-84-3; $CH_3CH(OCOC_6H_5)CH_2OH$, 51591-52-7; $CH_3CH(OCOC_6H_5)CH_2OCOC_6H_5$, 19224-26-1; $C_6H_5CH(OH)CH_2OCOC_6H_5$, 10335-95-2; $C_6H_5CH(OCOC_6H_5)CH_2OH$, 53574-78-0; $C_6H_5CH(OCOC_6H_5)CH_2OCOC_6H_5$, 7717-61-5; $CH_3CH(OH)CH_2CH_2OCOC_6H_5$, 59694-08-5; $CH_3CH(OCOC_6H_5)CH_2CH_2OCOC_6H_5$, 2867-65-4; n-$C_3H_7CH(OH)CH(C_2H_5)CH_2OCOC_6H_5$, 95647-73-7; methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, 3162-96-7; methyl 4,6-*O*-benzylidene-α-D-altropyranoside, 5328-47-2; methyl 4,6-*O*-benzylidene-β-D-glucopyranoside, 14155-23-8; methyl 4,6-*O*-benzylidene-2-*O*-benzoyl-α-D-glucopyranoside, 28642-64-0; methyl 4,6-*O*-benzylidene-3-*O*-benzoyl-α-D-glucopyranoside, 33535-04-5; methyl 4,6-*O*-benzylidene-2,3-*O*-dibenzoyl-α-D-glucopyranoside, 6748-91-0; methyl 4,6-*O*-benzylidene-2-*O*-benzoyl-α-D-altropyranoside, 35823-97-3; methyl 4,6-*O*-benzylidene-2-*O*-benzoyl-β-D-glucopyranoside, 38992-99-3; methyl 4,6-*O*-benzylidene-3-*O*-benzoyl-β-D-glucopyranoside, 38993-00-9; 1-(benzoyloxy)benzotriazole, 54769-36-7; 1-hydroxybenzotriazole, 2592-95-2; benzoyl chloride, 98-88-4.

Synthesis and Absolute Configuration of (*R*)- and (*S*)-Ethyl 3-(4-Oxocyclohex-2-enyl)propionate

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The importance of 4-substituted cyclohex-2-en-1-ones as synthetic starting materials continues to attract attention;[1] however, the preparation of relatively few optically active members of this group have been described.[2] In pursuing a synthesis of the cannabinoid derived analgetic CP-55,940,[3] we sought an efficient preparation of resolved alkyl 3-(4-oxocyclohex-2-enyl)propionate ((*S*)-**1**).[4] The synthesis of each enantiomer of this compound along with assignment of their absolute configuration is the subject of this note.

Due to the potential for racemization through enolization at the asymmetric center in **1**, we sought a route which would allow for initial resolution of that center while in protected form and also which would lend itself to eventual asymmetric synthesis. A strategy related to that of Birch[5] for the preparation of 4,4-disubstituted cyclohex-2-en-1-ones through fragmentation of bicyclo[2.2.2]octenes which were derived in turn from a Diels–Alder reaction fulfilled both our requirements.

Hydrolysis of the commercially available Diels–Alder adduct *endo/exo*-methyl 1-methoxybicyclo[2.2.2]oct-5-ene-2-carboxylate provided *rac*-**2** as a mixture of isomers.[6]

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