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Benzhydryl as an Efficient Selective Nitrogen Protecting Group for Uracils

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Abstract: Regioselective N-substitution of the less active nitrogen within uracil analogues has been achieved following preliminary N-protection at the more active N-position with a benzhydryl protecting group. This protecting group is stable to concentrated HCl (aqueous) at reflux temperature, TFA at room temperature, and Pd−C-catalyzed normal pressure hydrogenation at room temperature; the benzhydryl group can be removed quantitatively and selectively with a 10% triflic acid solution in TFA at 0 °C.

Direct substitution at the nitrogen positions of uracil analogues may yield the disubstituted product, the product monosubstituted at the more active N-position, or a complex mixture of mono- and disubstituted products. Selective protection/deprotection of the more active nitrogen is critical for the synthesis of uracil analogues monosubstituted at the less active nitrogen. A number of protecting groups have been proposed and used for the protection of endocyclic nitrogen atoms within uracils: acyl,[1] benzyl,[2] *p*-methoxylbenzyl (PMB),[3] alkoxymethyl,[4] alkoxycarbonyl,[5] and benzyloxycarbonyloxymethyl.[6] However, these protecting groups suffer significant limitations. For example, acyl-protected uracil analogues are susceptible to the ongoing reaction conditions, the benzyl group requires demanding reaction conditions for removal,[7] *tert*-butoxylcarbonyl (BOC)-protected uracil analogues are very labile (and the introduction of BOC to 5-nitrouracil failed),[5] and the bis(trimethylsiloxy)ethoxymethyl group is expensive and requires harsh deprotection conditions (40% of HF at 70 °C for 1.5 h).[4a] Alternatively, amine or amide nitrogens can be protected using a benzhydryl group. A literature search indicates that only two papers have employed the use of a benzhydryl group for protection of uracil analogues. Martinez et al.[8] attempted to use the benzhydryl group to protect both the N1 and N3 positions of 5-nitrouracil but failed because of unsuccessful deprotection. Odijk et al.[9] employed the benzhydryl group to selectively protect the N1 position of 5-fluorouracil. The benzhydryl group was introduced in a low yield (40%) by converting 5-flurouracil into its anion (NaH/HMPT) and then reacting with benzhydryl chloride. The removal of the benzhydryl group was performed with palladium-catalyzed hydrogenation (3−4 atm) but proved to be inefficient and highly sensitive to the hydrogenation procedure. Herein, we report our studies on the use of the benzhydryl group as an efficient protecting group for uracil and uracil analogues and illustrate its application by the preparation of uracil analogues monobenzylated at the less active nitrogen.

Direct introduction of the benzhydryl group using the sodium salt of uracil or uracil analogues and benzhydryl bromide gave the monoprotected products in low yield, along with disubstituted uracils and the starting materials. However, monobenzhydrylated uracil analogues could be conveniently and regioselectivity prepared in excellent yield by the reaction of a uracil analogue with bis(trimethylsilyl)actamide (BSA) in acetonitrile, followed by treatment with benzhydryl bromide in the presence of a catalytic amount of I_2 or tetrabutylammonium iodide (Scheme 1).[10] The results are summarized in Table 1. The position of benzhydrylation was dependent on the steric properties at the uracil C6 position. If C6 is hydrogen, the benzhydryl group was introduced at the less sterically hindered N1 position; otherwise, the benzhydryl group was introduced at the N3 position. The regiochemistry of these derivatives was assessed by NOE experiments.

Reaction of benzhydryl-protected uracils **2a**−**h** with benzyl bromide in DMF in the presence of potassium carbonate gave benzylated derivatives **3a**−**h** in excellent yield,[11] as shown in Table 1.

Reports on removal of the benzhydryl group from an amide nitrogen are limited. Martinez[8] failed in the

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(10) **Representative Procedure.** To a suspension of thymine **1b** (1.26 g, 10.0 mmol) in acetonitrile (30 mL) was added bis(trimethylsilyl)actamide (6.2 mL, 25 mmol) under argon. After the reaction mixture became a clear solution (in several minutes), benzhydryl bromide (3.71 g, 15.0 mmol) and a catalytic amount of I_2 were added. The reaction solution was heated at reflux until all starting material was consumed. After cooling to room temperature, the mixture was concentrated on a rotary evaporator, diluted with 100 mL of ethyl acetate, and washed with 50 mL of H_2O. The organic phase was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography (hexane/ethyl acetate = 3:2) to give 1-benzhydrylthymine **2b** (2.78 g, 95%) as a white powder: mp 226−227 °C; ^{1}H NMR (500 MHz, DMSO) δ 1.71 (d, J = 0.69 Hz, 3H), 6.94 (s, 1H), 7.16−7.43 (m, 11H), 11.43 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 12.1, 61.0, 109.3, 127.9, 128.3, 128.8, 137.9, 138.2, 151.0, 163.6; HRMS calcd for $C_{18}H_{16}N_2O_2$ 292.1212, found 292.1211.

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SCHEME 1

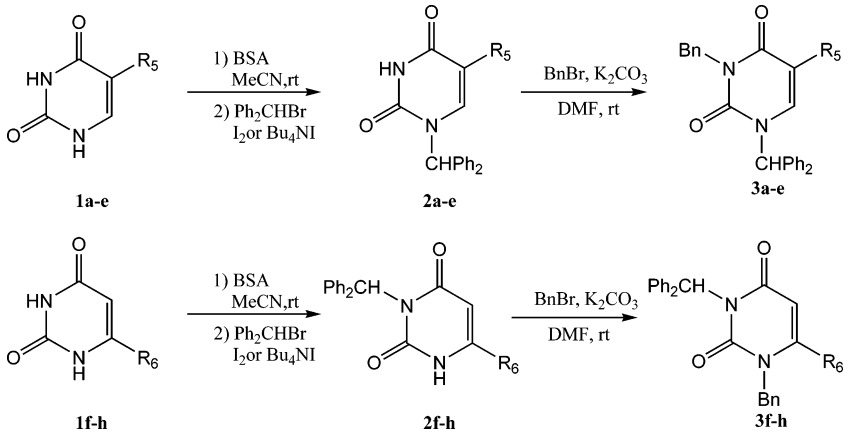

TABLE 1. Preparation of Benzhydryl Uracils 2 and Their Benzylation to 3

			product **2**			product **3**		
substrate **1**	R_5	R_6		yield (%)	mp (°C)		yield (%)	mp (°C)
1a	H		**2a**	80	212−213	**3a**	94	167−168
1b	Me		**2b**	95	226−227	**3b**	96	148−150
1c	Br		**2c**	81	214−216	**3c**	99	194−196
1d	NO_2		**2d**	72	262−263	**3d**	100	162−164
1e	F		**2e**	88	175−176[a]	**3e**	95	159−160
1f		*i*-Pr	**2f**	92	180−181	**3f**	95	146−147
1g		*n*-Bu	**2g**	55	135−136	**3g**	93	100−102
1h		Bn	**2h**	90	211−213	**3h**	100	169−171

[a] Lit.[9] mp 169−170 °C.

deprotection of the benzhydryl group from 5-aminouracil. Kita[12] achieved the deprotection of benzhydryl protected azetidine-2-one under Birch reduction conditions, but these conditions are not compatible with a *N*-benzyl group or with other reducible groups such as a bromo or nitro group. Wipf[13] effected the cleavage of the benzhydryl group in a quinone with TFA (at 50 °C overnight). Effenberger[14] used TFA for the deprotection of the benzhydryl group of oxoproline (at 70 °C for 40 h). We found that the benzhydryl group on uracils was stable to TFA at room temperature or concentrated HCl (aqueous) at reflux temperature and was only partially cleaved by TFA at refluxing temperature even after an extended reaction time. Effenberger[14] also effected the cleavage of the benzhydryl group from the oxoproline nitrogen by means of catalytic hydrogenation with $Pd(OH)_2/C$ in acetic acid at 40 °C for 85 h. Odijk et al.[9] used palladium-catalyzed hydrogenation (3−4 atm) for removal of the benzhydryl group in 5-fluorouracil, but this proved to be highly sensitive to the hydrogenation procedure. We found that the benzhydryl group on a uracil was only partially cleaved by Pd−C (or $Pd(OH)_2/C$)-catalyzed hydrogenation at 60 psi and room temperature or by hydrogenation at normal pressure in methanol, THF, or acetic acid at refluxing temperature. Therefore, the deprotection of benzhydyl-protected uracil analogues was further investigated. We found that the benzhydyl group was deprotected quantitatively and selectively in less than 30 min with a 10% triflic acid solution in TFA at 0 °C, without any affect on the benzyl group or other functional groups on the uracil analogues (Scheme 2 and Table 2).[15]

To further study the compatibility of the deprotection conditions with other function groups, several N3-

SCHEME 2

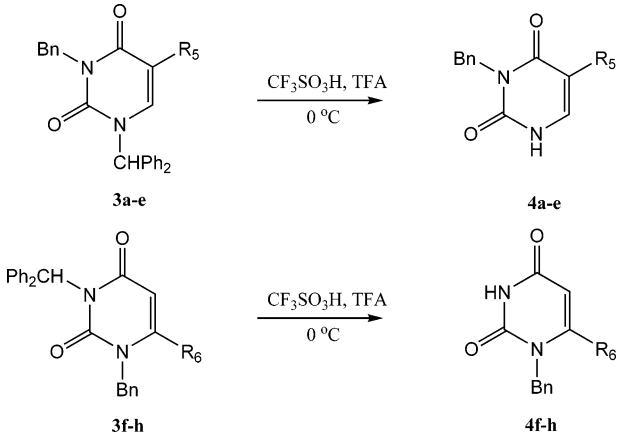

TABLE 2. Deprotection of Benzhydryl-Protected Uracils 3

substrate **3**	R_5	R_6	product **4**	yield (%)	mp (°C) observed	mp (°C) literature
3a	H		**4a**	100	181−182	177−178[4a]
3b	Me		**4b**	100	208−210 (dec)	200−202[4a]
3c	Br		**4c**	100	196−198 (dec)	160−161[4a]
3d	NO_2		**4d**	100	234−236 (dec)	222−224[4a]
3e	F		**4e**	100	157−159	156−157[16]
3f		*i*-Pr	**4f**	100	177−178	
3g		*n*-Bu	**4g**	100	121−122	
3h		Bn	**4h**	100	208−210 (dec)	

(11) **Representative Procedure.** To a suspension of 1-benzhydrylthymine **2b** (1.46 g, 5.0 mmol) and potassium carbonate (0.83 g, 6.0 mmol) in DMF (8 mL) under argon was added benzyl bromide (0.90 mL, 7.5 mmol) at room temperature. The mixture was stirred overnight at room temperature, diluted with ether (50 mL), washed with water (2 × 30 mL), dried over Na_2SO_4, and evaporated to dryness. The crude product was purified by flash chromatography (hexane/ethyl acetate = 5:1) to give 1-benzhydryl-3-benzylthymine **3b** (1.83 g, 96%) as a white powder: mp 148−150 °C; ^{1}H NMR (500 MHz, DMSO) δ 1.78 (d, J = 0.67 Hz, 3H), 5.03 (s, 2H), 7.01 (s, 1H), 7.21−7.43 (m, 16H); ^{13}C NMR (125 MHz, DMSO) δ 12.7, 44.0, 62.4, 108.6, 127.0, 127.4, 128.0, 128.2, 128.3, 128.8, 136.9, 137.0, 138.0, 151.2, 162.5; HRMS calcd for $C_{25}H_{22}N_2O_2$ 382.1681, found 382.1673.

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SCHEME 3

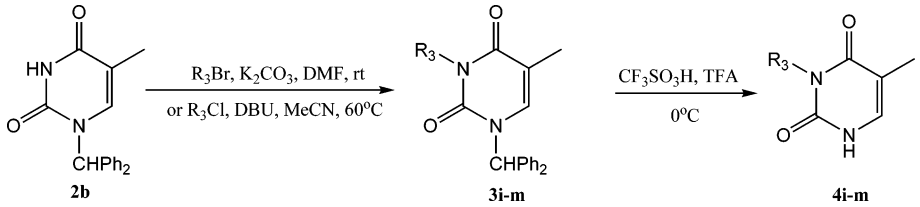

TABLE 3. Preparation of N3-Substituted 1-Benzhydrylthymines 3 and Their Deprotection

	product **3**			product **4**		
R_3		yield (%)	mp (°C)		yield (%)	mp (°C)
$EtOCOCH_2$-	**3i**	92	119−120	**4i**	100	156−158
p-CN-$C_6H_4CH_2$-	**3j**	95	148−149	**4j**	100	244−246
o-CF_3-$C_6H_4CH_2$-	**3k**	90	192−194	**4k**	100	143−144
m-MeO-$C_6H_4CH_2$-	**3l**	96	120−121	**4l**	100[a]	150−152
p-Br-$C_6H_4COCH_2$-	**3m**	90	193−195	**4m**	100	210−212

[a] Five equivalents of anisole was added to trap the benzhydryl cation formed in the deprotection and prevent benzhydrylation of the methoxybenzene ring in the product.

substituted 1-benzhydrylthymine derivatives were prepared and their deprotections were studied (Scheme 3 and Table 3). It was found that the benzhydryl groups were selectively cleaved and that the ester, ketone, ether, trifluoromethyl, and cyano groups were stable to those deprotection conditions.

In conclusion, as a protecting group for uracils, the benzhydryl group offers an alternative to other protecting groups by its easy introduction, stability to ongoing reaction conditions, and selective deprotection under mild condition.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of all compounds and 1D NOE spectra of compounds **2a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) **Representative Procedure.** To an ice-cooled solution of triflic acid (0.5 mL) in TFA (5 mL) was added 1-benzhydryl-3-benzylthymine **3b** (764 mg, 2.0 mmol). The mixture was stirred at 0 °C for 30 min. TLC showed that all starting material was consumed. The reaction mixture was slowly poured onto 50 g of ice water. After warming to room temperature, the white precipitate was collected by filtration. The crude product was purified by flash chromatography (ethyl acetate/hexane = 2:1) to give 3-benzylthymine **4b** (432 mg, 100%) as a white powder: mp 208−210 °C; ^1H NMR (500 MHz, DMSO) δ 1.79 (d, J = 0.86 Hz, 3H), 4.96 (s, 2H), 7.22−7.31 (m, 5H), 7.35 (d, J = 4.34 Hz, 1H), 10.99 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 12.3, 42.7, 107.2, 126.9, 127.5, 128.2, 136.4, 137.4, 151.3, 163.7; HRMS calcd for $C_{12}H_{12}N_2O_2$ 216.0899, found 216.0895.

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