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Steric hindrance is a key factor in the coupling reaction of (acyloxy) alkyl-α-halides with phenols to make a new promoiety for prodrugs

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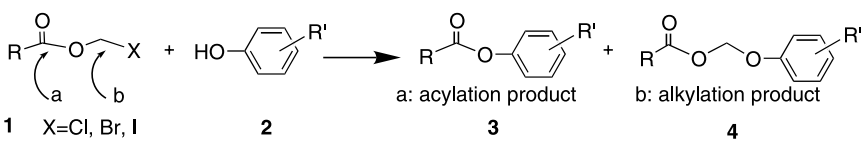
Abstract—A convenient and mild method for the synthesis of various (acyloxy) alkyl-α-ethers of phenols was described. (Acyloxy) alkyl-α-halides were conjugated with phenols in acetone in the presence of cesium carbonate to give (acyloxy) alkyl-α-ethers of phenols. Steric hindrance is a key factor governing this reaction and greater steric hindrance favors the alkylation product over the acylation product.

The (acyloxy) alkyl moiety has been widely used to prepare prodrugs for therapeutic agents containing carboxylic acid, amine, phosphate, and phosphonate groups.[1–4] However, there are only two methods available for the preparation of (acyloxy) alkyl ether prodrugs **4** of phenol.[5–7] The first involves the coupling of a carboxylic acid with a haloalkyl ether of phenol.[5] However, one of the reactants, the haloalkyl ether of phenol, has to be synthesized in very harsh conditions,[8–11] which renders this method non-applicable to phenols sensitive to high temperature. The second method involves the coupling of (acyloxy) alkyl-α-halides **1** with phenol **2** (Scheme 1). Unfortunately, the hydroxyl oxygen of phenol **2** can attack the carbonyl carbon atom (path a) as well as the halo-carbon atom (path b) to give acylation product **3** and alkylation product **4**, respectively. Sloan and Kohn reported that the product distribution obtained from the reaction of halide **1** with phenol **2** depended on the nucleophilicity of the phenol and the nucleofugicity of the leaving halo-atom.[6] A more nucleophilic phenol favors the formation of the acylation product **3** while a better leaving group in halide **1** produces more of the alkylating product.[6] In this study, we found a convenient and mild method to synthesize (acyloxy) alkyl-α-ethers of phenol **4**; the steric effect was found to be a key factor governing the product distribution of this reaction.

Our initial studies were directed to the coupling reaction of Alloc-D-Leu-OCH_2I **1a** with phenol **2a** as part of an effort to make a peptide prodrug containing an (acyloxy) alkyl-α-ether of the phenol moiety (Scheme 2).[12,13] However, all reported coupling methods[7,14,15] failed to produce the desired product **4** and only the undesirable acylation product (path a) was obtained. After reviewing the literature, we found that successful coupling reactions that generate alkylation product **4** (path b) had been achieved with three representative (acyloxy) alkyl-α-halides, namely 3-halo-2-(5*H*)-furanone, 3-halo-1-(3*H*)-isobenzofuranone and (pivalyloxyl) methyl halide.[6,7,14,15] These (acyloxy) alkyl-α-halides either have a substituted α-halo-carbon atom or have a *t*-butyl group directly connected to the



Scheme 1. The coupling reaction of (acyloxy) alkyl-α-halide **1** with phenol **2**.

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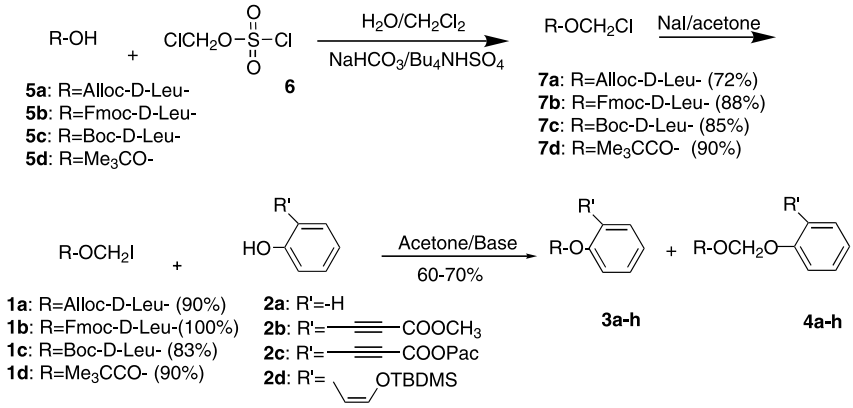

Scheme 2. The synthesis of acyl phenols **3** and (acyloxy) alkyl phenols **4**.

carbonyl carbon atom. Therefore, our hypothesis was that the steric effect of the α-amino protecting group of the leucine amino acid and the *ortho* group of the phenol **2** might play a major role in the coupling reaction to favor product **4**.

The hypothesis was tested by studying the product distribution of the coupling reaction between **1** and phenols **2**. As shown in Scheme 2, various groups (i.e. Alloc-, Fmoc-, and Boc-) were used to protect the N-terminal of leucine with different sizes for steric effects. Compounds **5a**–**c** and **5d** were transformed into chlorides **7a**–**d** using chloromethyl chlorosulfate **6**[16,17] in a two-phase system of dichloromethane and aqueous sodium bicarbonate in the presence of a phase transfer agent (i.e. n-Bu_4NHSO_4). This reaction gave a good yield (71.8–90.3%). Direct reaction between chlorides **7a**–**c** and phenol **2a** produced only acylation products (data not shown). Reaction of chlorides **7a**–**d** with sodium iodide in acetone gave iodides **1a**–**d**; coupling of **1a**–**d** with phenols **2a**–**d** in the presence of carbonate salts gave both acylation and alkylation products in different ratios (Table 1).

The product distribution of the coupling reaction of R-OCH_2I **1** with phenols **2** (Table 1) indicates that steric hindrance is a key factor governing the coupling reaction of (acyloxy) alkyl-α-halides with phenols. When the protecting groups of N-terminal-protected (leucyloxy) methyl iodides **1a**–**c** were changed from the relatively small Alloc- to the bulkier Fmoc- and Boc-, the reaction of **1a**–**c** with phenol **2a** generated an increasing proportion of the alkylation products **4a**–**c** (i.e. 5, 10, and 15%, respectively) with K_2CO_3 as a base. Under the same conditions, the reaction of **1c** with *ortho* alkynyl-substituted phenol **2b** gave 38% of alkylation product **4d**. These results suggested that steric hindrance from both (acyloxy) alkyl-α-halides and phenols increases the percentage of alkylation product. Furthermore, when cesium carbonate was employed instead of potassium carbonate,[18] the reaction of **1c** with **2b** gave an even higher percentage of alkylation product **4e** (53%) and the reaction was completed in 2 h at 0°C rather than 12 h at room temperature. With cesium carbonate as a base, the reaction of Boc-D-Leu-OCH_2I **1c** with phenols **2c** and **2d** gave 58 and 28% of alkylation products **4f**–**g**, respectively, indicating that

Table 1. The product distribution of the coupling reaction between R-OCH_2I **1** and phenols **2**[19,a]

	R	R'	Base	**3** (%)	**4** (%)
a	Alloc-D-Leu	H	K_2CO_3	95	5
b	Fmoc-D-Leu	H	K_2CO_3	90	10
c	Boc-D-Leu	H	K_2CO_3	85	15
d	Boc-D-Leu	$-C\equiv C-COOCH_3$	K_2CO_3	62	38
e	Boc-D-Leu	$-C\equiv C-COOCH_3$	Cs_2CO_3	47	53
f	Boc-D-Leu	$-C\equiv C-COOPac$	Cs_2CO_3	42	58
g	Boc-D-Leu	OTBDMS	Cs_2CO_3	72	28
h	$(CH_3)_3CO$	H	Cs_2CO_3	--	100

[a] Abbreviations: Alloc, allyloxy carbonyl; Leu, leucine; Fmoc, 9-fluorenylmethoxy carbonyl; Boc, t-butoxy carbonyl; Pac, phenacyl; TBDMS, t-butyldimethylsilyl.

the steric effect of an alkynyl substitution on the *ortho*-position of phenol is probably more significant than that of an alkenyl group. Furthermore, phenol **2c** has lower nucleophilicity than phenol **2d** because the alkynyl group in phenol **2c** is more electron withdrawing than the alkenyl group in **2d**. Thus, the low nucleophilicity of phenol **2c** prefers the alkylation reaction (path b) over the acylation reaction (path a), which is consistent with the previous observation by Sloan and Kohn.[6]

Finally, the coupling reaction of (pivalyloxy) methyl iodide **1d** with phenol **2a** was studied. Since the carbonyl carbon atom in the (acyloxy) alkyl moiety is the electrophilic center involved in acylation reaction (path a), steric hindrance to this atom would decrease the acylation product and consequently increase the percentage of the alkylation product (path b). The *t*-butyl group of (pivalyloxy) methyl iodide **1d** is directly attached to the carbonyl carbon atom; thus, its steric effect should be much more significant than that of the *t*-butyl group of Boc-D-Leu-OCH_2I **1c**, which is several atoms away from the carbonyl carbon atom. The fact that coupling of **1d** with **2a** gave only alkylation product **4h** further confirmed our hypothesis.

In summary, the method described above provides a mild and rapid way to synthesize (acyloxy) alkyl-α-ethers of phenol **4** via coupling (acyloxy) alkyl-α-halide **1** with phenol **2**. Steric hindrance is a key factor governing the product distribution and greater steric hindrance favors alkylation product **4** over acylation product **3**.

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19. Typical procedures: A mixture of phenol (**2**) (1 mmol) and base (1 mmol) in anhydrous acetone (5 ml) was stirred at 0°C. After 30 min, R-OCH_2I (**1**) (1 mmol) was added and the mixture was maintained at room temperature for another 12 h (2 h when using Cs_2CO_3). Acetone was removed in vacuo. The residue was taken up with dichloromethane (20 ml) and filtered. The filtrate was condensed and the residue was purified by silica gel chromatography. Total conversion rate of this reaction is 60–70% for all entries (the separated yield). For entries a–d, compounds **3** and **4** were not separated and the product distribution was determined by NMR. For entries f–h, compounds **3** and **4** were separated and the product distribution was determined by calculating their molar percentages.