

Reaction of alkylcarbonyloxymethyl halides with phenols: reevaluating the influence of steric hindrance

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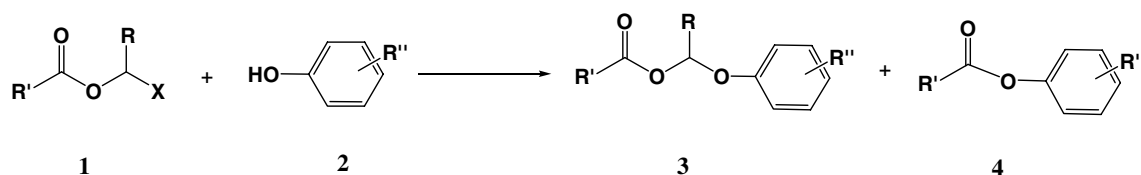
Abstract—Evidence is presented that contradicts an earlier finding that, in the absence of steric hindrance, the coupling reaction of alkylcarbonyloxymethyl (ACOM) halides with phenols favors acylated product. A one-step synthesis is used to generate sterically unhindered ACOM iodides, which are then reacted with several phenols to give mainly alkylated phenol.

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It has been known for quite some time that ACOM halides **1** display an ambient reactivity—sometimes nucleophiles react at the carbonyl to give acylated products, while at other times the alkyl halide carbon is attacked to give alkylated products (Scheme 1). In the initial report on the reactions of ACOM halides **1** with phenols **2**,¹ it was noted that the nucleophilicity of **2** and the nucleofugicity of the halide in **1** are the key determinants of the product distribution. Recently, Ouyang et al. have suggested that both **1** and **2** must be sterically hindered in order to shift the product distribution in favor of **3**.² The conclusions of Ouyang et al.² were based on the reactions of **1** with **2**, where R' was an N-protected leucine derivative. For example, when R' was Alloc-D-Leu (Table 1, entry 1), the product distribution was shifted

almost entirely toward acylated phenol **4**. However, when both the protecting group and the phenol were sterically hindered (Table 1, entry 2), the percentage of alkylated phenol **3** increased substantially. Although only one aliphatic ACOM iodide was examined² (i.e., R = H, R' = (CH₃)₃C, **2** = phenol), the authors argued that steric hindrance was essential for the successful coupling of **1** with **2** regardless of whether R' was aliphatic or an amino acid.

As part of our work in developing a prodrug database from which flux through skin may be modeled,³ we were interested in synthesizing a homologous series of ACOM prodrugs of 4-hydroxyacetanilide (acetaminophen, or APAP), a sterically unhindered model phenol,



X = Cl, Br, I
R = H, alkyl
R' = alkyl, aryl, etc.
R'' = alkyl, aryl, etc.

Scheme 1. Reaction of ACOM halides **1** with phenols **2**.

Keywords: Steric hindrance; Alkylcarbonyloxymethyl halide; Phenol; Prodrug.

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Table 1. Product distribution^a of the reaction^b of ACOM iodides **1** with phenols **2**^c

Entry	1	+	2 \longrightarrow	Distribution (%)	
				3	4
1		+		5	95
2		+		38	62
3		+		63	37
4		+		73	24

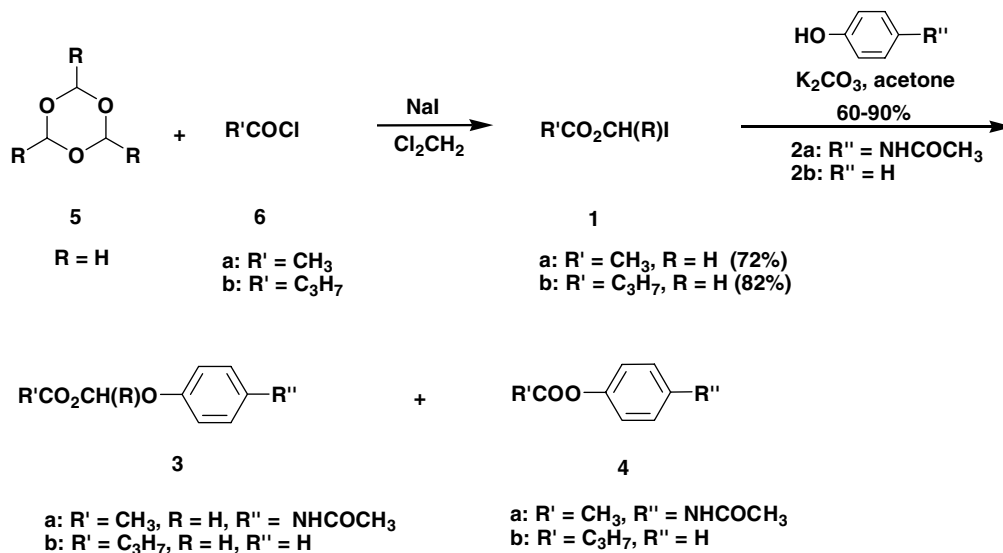
^a Product distribution determined from ¹H NMR spectrum of the crude reaction mixture.

^b Reaction conditions: base = K₂CO₃ (all entries), solvent = acetone (entries 1 and 2) or acetonitrile (entries 3 and 4), room temperature.

^c Data in entries 1 and 2 from Ref. 2. Data in entries 3 and 4 from the present work.

though it was unclear whether sterically unhindered ACOM derivatives of APAP could be synthesized given the report of Ouyang et al.² First, we required synthetic routes to **1** that allowed X = I, R = H, and R' = short-chain aliphatic groups.⁴ This was accomplished by adopting the method of Fleischmann et al.⁵ to the present case. By this approach, compounds **1a** and **1b** were synthesized in one step and in a good yield starting from trioxane **5** and acid chlorides **6** in the presence of NaI⁶ (Scheme 2).⁷ Compounds **1a** and **1b** were then reacted with various phenols using a standard protocol¹ to obtain various percentages of **3** and **4**.⁸

If steric hindrance is a key determinant of product distribution as postulated by Ouyang,² then the coupling of short-chain aliphatic ACOM iodides with sterically unhindered phenols should generate mainly acylated product **4**. This did not occur. On the contrary, for the straight-chain ACOM derivatives studied here, **3** was the major product in every case regardless of the steric hindrance presented by **2** or **1**. The only instance where **4** formed in preference to **3** was when chloride was used as the leaving group X⁹—a result that agrees with an earlier study.¹ It should also be noted that others^{10,11} have found that the good yields of **3** may be obtained

**Scheme 2.** Synthesis of ACOM iodides **1** and subsequent reactions of **1** with phenols **2**.

under essentially the same conditions used by Ouyang et al.² but from sterically *unhindered* ACOM halides (X = Br or I). The weak dependence of the product distribution on steric hindrance when R' is aliphatic is most apparent when comparing entries 3 and 4 with entries 1 and 2 (Table 1). In these cases, sterically unhindered **1** and **2** (entries 3 and 4) gave higher percentages of **3** than sterically hindered **1** and **2** (entries 1 and 2). Evidently, amino acid-derived ACOM iodides exhibited a different reactivity with phenols than carboxylic acid-derived ACOM iodides.

In conclusion, steric hindrance does not appear to be a 'key' determinate of product distribution when R' = aliphatic, contrary to the assertions of Ouyang et al. As the assertions of Ouyang et al.² is the only report, where R' is a protected amino acid, such ACOM halides may react with phenols by a different mechanism than that described¹ for the simple derivatives of **1** (i.e., where R' = aliphatic).

References and notes

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4. The most common synthetic route to short-chain ACOM iodides is a typically low-yielding, two-step synthesis. See Iyer, R.; Yu, D.; Ho, N.; Agrawal, S. *Synth. Commun.* **1995**, *25*, 2739–2749, for examples.
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6. In some cases, the addition of AlCl₃ (0.1 mol %) and I₂ (0.02 mol %) to the reaction mixture was necessary to achieve good yields of ACOM iodide.
7. In order to minimize exposure to potentially toxic products, no effort was made to purify **1a** and **1b** before their use in coupling reactions with phenols. Thus, crude **1a** and **1b** used in the coupling reactions contained 6–19% ACOM chloride and 3–11% bis(alkylcarbonyloxy)methane; no acid halide remained. All compounds in the mixture gave ¹H NMR spectra that were consistent with the previously reported spectra (see Ref. 4). Crude yield was calculated on the basis of the mole ratio of the products as determined by ¹H NMR. Note: the percentage of **4** in the reaction mixture did not increase significantly as the percentage of ACOM chloride (within the range of 6–19%) in crude **1** increased.
8. Compounds **3** and **4** were separated by column chromatography on silica gel. 4-Butyloxymethylacetanilide (**3b**) as a representative: 25% yield; mp = 56–58 °C; one spot on TLC (EtOAc/hexane, 1:1) R_f 0.16; ¹H NMR (CDCl₃) δ 7.42 (d, J = 8 Hz, 2H), δ 7.13 (br s, 1H), δ 6.99 (d, J = 8 Hz, 2H), δ 5.74 (s, 2H), δ 2.34 (t, J = 7 Hz, 2H), δ 2.17 (s, 3H), δ 1.65 (m, 2H), δ 0.94 (t, J = 7 Hz, 3H); Anal. Calcd for C₁₃H₁₇NO₄: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.92; H, 6.85; N, 5.52.
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