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Overcoming steric effects in the coupling reaction of alkyloxycarbonyloxymethyl (AOCOM) halides with phenols: an efficient synthesis of AOCOM phenolic prodrugs

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Abstract—Steric hindrance is a key factor in the coupling reaction of AOCOM halides with phenols. Sterically unhindered alkoxy groups favor the formation of acylated phenol. Under phase-transfer conditions, alkylated phenol is favored regardless of steric hindrance.

Alkyloxycarbonyloxymethyl (AOCOM) prodrugs are members of a class of 'soft alkyl'[1] derivatives of active drugs that are often used to overcome bioavailability problems related to stability and solubility.[2] Given the prevalence of the phenolic functional group in biological and pharmaceutical compounds, there are surprisingly few examples in the literature of AOCOM prodrugs of phenol. Although the synthesis of some AOCOM ethers of phenol has been reported in the patent literature,[3–5] we are aware of only one report of this technique being applied to a phenol for the purpose of prodrug derivatization.[6] In that study, Seki et al. note that 4-ethoxycarbonyloxymethylacetanilide was obtained in a 20% yield from the coupling of 4-hydroxyacetanilide with ethoxycarbonyloxymethyl iodide following a reaction time of seven days. In an effort to improve the yield and ascertain the reaction parameters by which this reaction is governed, we have synthesized a series of AOCOM derivatives of 4-hydroxyacetanilide, a model phenol, by Seki's method[6] and by a more efficient method involving phase-transfer catalysis (PTC). Although the synthesis of AOCOM ethers of phenol via PTC is unprecedented, others[7–9] have shown that PTC formation of phenolic ethers is applicable to a broad range of phenols and alkylating agents.[10] Sloan and Koch[11] briefly mention in their report that the reaction of pivalyloxymethyl chloride with phenol gave only acylated product under PTC conditions. However, Wolff and Hoffman[9] have successfully coupled 5-bromo-2(5*H*)-furanones with phenols under PTC conditions. Thus it was of interest to determine whether PTC could improve the yield of **3** in the present case. We have compared our results to those obtained from the coupling reaction of ACOM halides with phenols—an analogous system whose reaction parameters are known[11,12] (Scheme 1).

In the present investigation, 4-hydroxyacetanilide (APAP) was chosen as a model phenol in order to make a direct comparison between this work and the work of Seki et al.[6] As shown in Scheme 2, AOCOM iodides may be obtained from the corresponding chlorides via halogen exchange in acetone. A subsequent reaction with phenols under standard conditions (acetonitrile or acetone as the solvent, K_2CO_3 as the base)[6,11] or in a biphasic system in the presence of tetrabutylammonium hydrogen sulfate (Scheme 2) gave mixtures of **3** and **4**.

Although the data presented in Table 1 is not exhaustive, it suggests that the trends observed in the reactions of ACOM halides with phenols[11,12] are operative in the analogous reactions of AOCOM halides. For example, under the standard conditions, if X is a poor leaving group, **4** is favored, but as the nucleofugicity of X increases, the product distribution shifts toward **3**

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

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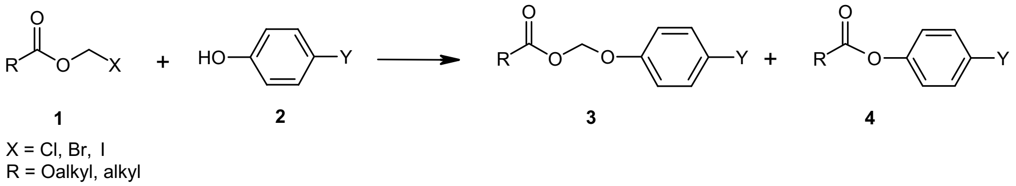
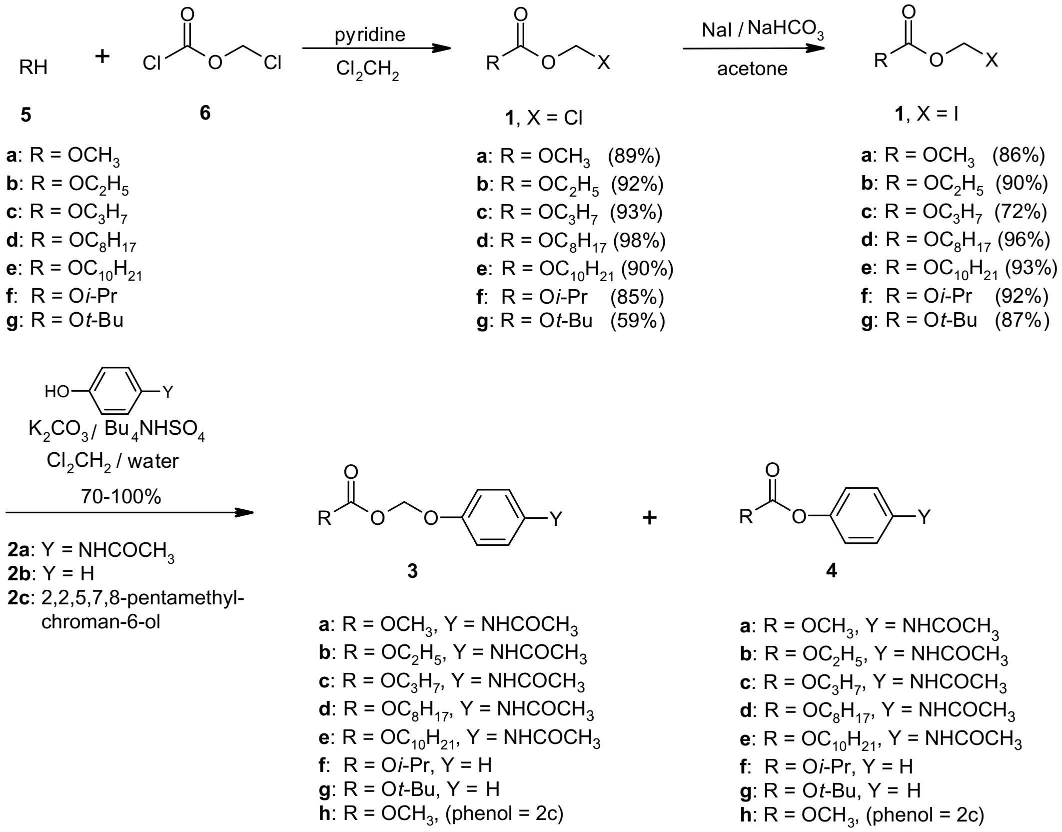


Scheme 1. Generalized reaction of AOCOM halides (R = Oalkyl) and ACOM halides (R = alkyl) **1** with phenols **2**.



Scheme 2. Reaction of AOCOM iodides with phenols under phase-transfer conditions.

(compare entries 1 and 2 with 4). In addition, for X = I, alkylated phenol **3** becomes the major product when the alkoxy chain length extends beyond OCH_3.

The ratio **4**/**3** for R = OCH_3 drops by 70% when the reaction is carried out under phase-transfer conditions instead of the standard protocol (entry 3 vs entry 6). Under these conditions, there is an incremental increase in percentage of **3** with increasing steric hindrance (as measured by Charton's steric parameters[13]) in R (entries 6–8), but beyond propyloxy, the percentage of **3** remains fairly constant for the straight chain derivatives studied. However, the product distribution shifts entirely toward **3** on going to more bulky R groups (entries 11–12). The percentage of **3** may also be increased for sterically unhindered R if the phenol is sufficiently hindered (entry 6 vs entry 13). This particular result (entry 13) is not without precedent since others[12,14] have observed a similar trend in the reactions of ACOM halides with phenols. Aside from its effect on product distribution, the advantages of the phase-transfer reaction include shorter reaction times (one day) and a higher overall yield[15] compared to the standard protocol (i.e., the method used by Seki et al.).[6]

As noted by previous investigators,[11,12] ACOM halides react with phenols under the standard conditions to give mainly **3** (where R = alkyl) as long as X is a good leaving group (⩾Br). The relatively high ratio **4**/**3** in the AOCOM series compared to the ACOM series both using standard conditions (compare entries 3–5 with entries 14 and 15) was unanticipated, since the carbonyl of a carbonate is usually less reactive than the carbonyl of the corresponding ester.[16] Thus one might expect less acylation when R is alkyloxy (as in AOCOM) than when it is alkyl (as in ACOM).[17] On the other hand, the analysis of the steric parameters for both series (ACOM and AOCOM) suggests that differences in **4**/**3** between the series are related to the differences in the steric hindrance of R based on Charton's steric parameters (compare

Table 1. Product distribution of the reaction of RCO_2CH_2X **1** with phenols **2** under various reaction conditions

Entry	R	X	Phenol	Solvent	Base	Distribution[a] (%)		v[b]
						3	**4**	
1	OC_2H_5	$[MeNC_4H_8]^+$	**2a**	Acetonitrile	$MeNC_4H_8$	0	100 (28)[c]	0.48[d]
2[e]	OC_2H_5	Cl	**2a**	Acetonitrile	K_2CO_3	3	58	
3	OCH_3	I	**2a**	Acetonitrile	K_2CO_3	36	64	0.36[d]
4	OC_2H_5	I	**2a**	Acetone	K_2CO_3	57 (17)[c]	43 (13)[c]	
5	OC_4H_9	I	**2a**	Acetone	K_2CO_3	58	42	0.58[d]
6[f]	OCH_3	I	**2a**	Cl_2CH_2/H_2O	K_2CO_3	66 (18)[c]	34 (6)[c]	
7[f]	OC_2H_5	I	**2a**	Cl_2CH_2/H_2O	K_2CO_3	74 (50)[c]	26 (13)[c]	
8[f]	OC_3H_7	I	**2a**	Cl_2CH_2/H_2O	K_2CO_3	84 (43)[c]	16 (6)[c]	0.56[d]
9[f]	OC_8H_{17}	I	**2a**	Cl_2CH_2/H_2O	K_2CO_3	82 (45)[c]	18 (3)[c]	0.61[d]
10[f]	$OC_{10}H_{21}$	I	**2a**	Cl_2CH_2/H_2O	K_2CO_3	78 (41)[c]	22 (6)[c]	0.56[g]
11[f]	O-*i*-Pr	I	**2b**	Cl_2CH_2/H_2O	K_2CO_3	100	0	0.75[d]
12[f]	O-*t*-Bu	I	**2b**	Cl_2CH_2/H_2O	K_2CO_3	100	0	1.22[d]
13[f]	OCH_3	I	**2c**	Cl_2CH_2/H_2O	K_2CO_3	90 (33)[c]	10 (0)[c]	
14[h]	CH_3	I	**2b**	Acetonitrile	K_2CO_3	63	37	0.52[i]
15[h]	C_3H_7	I	**2a**	Acetonitrile	K_2CO_3	73	24	0.68[i]

[a] Determined from the ^1H NMR spectrum of the crude reaction mixture.

[b] Charton's steric parameter for R.

[c] Isolated yield of analytically pure compound.

[d] Ref. 13.

[e] Product mixture also contains approx. 39% unidentified material.

[f] Reaction mixture includes 1 equiv tetrabutylammonium hydrogen sulfate.

[g] Estimated from the relationship $v = 0.406n_\beta + 0.108n_\gamma + 0.059n_\delta - 0.00839$ in Charton, M. *J. Org. Chem.* **1978**, *43*, 3995–4001.

[h] Ref. 12.

[i] Ref. 18.

entries 3–5 to entries 14 and 15).[13,18] A plot v versus the ratio of **4**/**3** observed under PTC (entries 6–11) is shown in Figure 1.

At present, it is unclear why the product distribution shifts toward **3** under PTC. However, the results are most likely related to the nature of the ion-pair generated under these conditions. Previously, Ouyang et al. found that **4**/**3** (where R = alkyl) decreased when K_2CO_3 was replaced with Cs_2CO_3 in the reactions of ACOM iodides with phenols.[14] In both cases, the change in cation ($K^+ \rightarrow Bu_4N^+$ in this work and $K^+ \rightarrow Cs^+$ in the work of Ouyang) results in a phenolate anion that is less associated with its counterion and hence more reactive.[19,20] Thus the observed decrease in **4**/**3** may be due to a faster reaction at the alkyl halide (to give **3**) than at the carbonyl (to give **4**). The increased yield and decreased reaction time under PTC may also be due to the increased reactivity of the phenolate anion as well.

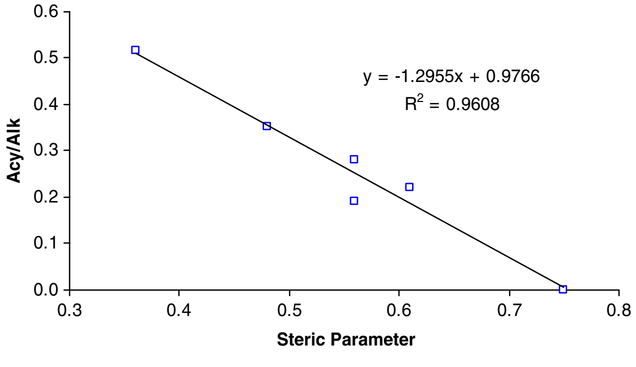


Figure 1. Plot of Charton's steric parameter v for R versus the ratio of acylated/alkylated product (**4**/**3**) resulting from the reactions of **2** with AOCOM iodides (entries 6–11 in Table 1, □) under phase-transfer conditions.

In conclusion, the data presented here suggests that steric hindrance plays a greater role in the coupling reactions of AOCOM halides with phenols than in the analogous reactions of ACOM halides. However, this problem may be circumvented through the use of phase-transfer catalysis. Under these conditions, the influence of steric hindrance (as characterized by Charton's steric parameters) is minimized, reaction time is reduced, and overall yields are increased.

Supplementary data

Supplementary data associated with this article including experimental procedures and compound characterization can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.160.

References and notes

1. Sloan, K. B. Functional group considerations in the development of prodrug approaches to solving topical delivery problems. In *Prodrugs: Topical and Ocular Drug Delivery*; Sloan, K. B., Ed.; Marcel Dekker: New York, 1992; pp 17–116.
2. Beaumont, K.; Webster, R.; Gardner, I.; Dack, K. *Curr. Drug Metab.* **2003**, *4*, 461–485.
3. Johansson, N; Zhou, X.; Wahling, H.; Sund, C.; Wallberg, H.; Salvador, L.; Lindstrom, S. PTC Int. Appl., WO 9941275, 1999.

4. Zhou, X.; Johansson, N.; Wahling, H.; Sund, C.; Salvador, L.; Lindstrom, S.; Wallberg, H.; Sahlberg, C. U.S. Pat. Appl. Publ., US 2002128301, 2002.
5. Lohray, B.; Lohray, V.; Srivastava, B. PCT Int. Appl., WO 2003082864, 2003.
6. Seki, H.; Kawaguchi, T.; Higuchi, T. *J. Pharm. Sci.* **1988**, *77*, 855–860.
7. McKillop, A.; Fiaud, J.; Hug, R. *Tetrahedron* **1974**, *30*, 1379–1382.
8. van Heerden, F.; van Zyl, J.; Rall, G.; Brandt, E.; Roux, D. *Tetrahedron Lett.* **1978**, *19*, 661–662.
9. Wolff, S.; Hoffmann, H. *Synthesis* **1988**, *10*, 760–763.
10. Jones, R. *Quarternary Ammonium Salts: Their Use in Phase-Transfer Catalysis*; Academic Press: London, 2001.
11. Sloan, K. B.; Koch, S. *J. Org. Chem.* **1983**, *48*, 3777–3783.
12. Thomas, J.; Sloan, K. B. *Tetrahedron Lett.* **2006**, *47*, 8785–8787.
13. Charton, M. *J. Org. Chem.* **1977**, *42*, 3531–3535.
14. Ouyang, H.; Borchardt, R.; Siahaan, T. *Tetrahedron Lett.* **2002**, *43*, 577–579.
15. Compounds **3** and **4** were obtained in approximately 95% purity following column chromatography of the crude reaction mixture. This material was then recrystallized from various solvents to obtain analytically pure compounds in the yields shown in Table 1. The yields of the 95% pure material were on average 36% higher than those listed in Table 1 (see Supplementary data for details).
16. Smith, M.; March, J. Aliphatic nucleophilic substitution. In *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed.; Smith, M., March, J., Eds., John Wiley and Sons: New York, 2001; pp 389–675.
17. Since the AOCOM iodides **1** (X = I, R = Oalkyl) were not purified other than to filter off NaCl and unreacted NaI (see Experimental below), it is worth considering whether any remaining AOCOM chloride in crude **1** (X = I, R = Oalkyl) affected the product distribution. If **1** (X = Cl, R = Oalkyl) was reacting with **2** to any significant extent, then the percentage of acylated product **4** would have increased as the percentage of **1** (X = Cl, R = Oalkyl) increased. In the case of entries 3, 4, and 5, the percentages of unreacted AOCOM chloride **1** (X = Cl, R = Oalkyl) in crude **1** (X = I, R = Oalkyl) were 2%, 9%, and 9%, respectively. Thus, it does not appear that the product distribution was affected by the presence of AOCOM chloride in crude **1** (X = I, R = Oalkyl).
18. Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 1552–1556.
19. Landini, D.; Maia, A.; Montanari, F. *J. Am. Chem. Soc.* **1978**, *100*, 2796–2801.
20. Dijkstra, G.; Kruizinga, W.; Kellogg, R. *J. Org. Chem.* **1987**, *52*, 4230–4234.