Selective *ortho*-Substitution of Some Phenolic Compounds

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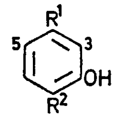
Summary Formylation and bromination of titanium tetrachloride complexes of some *o*-hydroxycarbonyl compounds occurs, to a large extent, at the 3-position.

We have found that titanium tetrachloride exerts a profound effect on the direction of electrophilic substitution in *o*-hydroxycarbonyl compounds. Bromination of the com-



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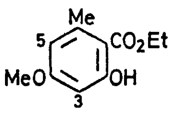


(2)

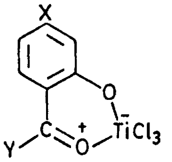
a; R^1 = OMe, R^2 = CO_2Me
b; R^1 = OH, R^2 = CO_2Me
c; R^1 = OMe, R^2 = CO Me
d; R^1 = Me, R^2 = CO_2Me

Table

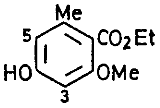
Substrate	$TiCl_4$ bromination[a,b]	Formylation[b]
(1a)	48% 3-Br	48% 3-formyl
	41% 5-Br	8% 5-formyl
(1b)	36% 3-Br	
	30% 5-Br	38% 3-formyl
	12% 3,5-Br_2[c]	
(1c)	65% 3-Br	32% 3-formyl
	15% 5-Br	2% 5-formyl
(1d)	32% 3-Br	32% 3-formyl
	48% 5-Br	5% 5-formyl
	4% 3,5-Br_2[c]	
(2)	40% 3-Br	49% 3-formyl
	40% 5-Br	5% 5-formyl

[a] Bromination without $TiCl_4$ gives only the 5-bromo-compound. Brominations with $TiCl_4$ were carried out by addition of $TiCl_4$ (12·5 mmol) to a stirred solution of the substrate (5 mmol) in CH_2Cl_2 (10 ml), followed by Br_2 (5 mmol). The solution was stirred for 5 min, then poured on to ice and water and stirred rapidly and then worked-up in the usual way. [b] % yields given. [c] Starting material was also isolated.

pounds in the Table gives exclusively the 5-bromo-compound. Under identical conditions except for the presence of an excess of titanium tetrachloride appreciable amounts of the 3-bromo-compounds result. Since $<$ 1 mol. equiv. of titanium tetrachloride reduces the amount of 3-bromination, a 1:1 complex of the *o*-hydroxycarbonyl compounds, such as (**3**), is clearly implicated.



(3) X = Me, OMe, or OH
Y = Me, or OMe



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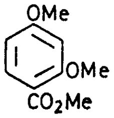

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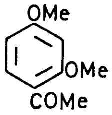

(6)

On formylation of these compounds using 1,1-dichlorodimethyl ether and an excess of titanium tetrachloride[1] the 3-formyl compounds are the major products. However formylation of compounds (**4**)—(**6**) occurs solely at the 5-position thus providing further evidence for the intermediacy of a complex such as (**3**).

Collman[2] has observed that transition-metal complexes of β-diketones undergo electrophilic substitution in a manner analogous to aromatic compounds. The occurrence of substitution at the 3-position in titanium tetrachloride complexes of *o*-hydroxycarbonyl compounds points to a degree of bond fixation in the benzene ring of these complexes, and by analogy with Collman's work, they may be regarded as having naphthalene-like character. Thus the metal chelate ring system behaves as a fused aromatic nucleus such that the 3-position constitutes the most reactive α-position of this naphthalenoid system.

This synthetic method is of obvious utility in the preparation of otherwise inaccessible compounds.

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[1] H. Gross, A. Rieche, and G. Matthey, *Chem. Ber.*, 1963, **96**, 308.

[2] J. P. Collman, *Angew. Chem.*, 1965, **77**, 154.