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# Photochemical Ethoxycarbonylmethylation of Anisole with Ethyl Chloroacetate in the Presence of Zinc Chloride

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**Synopsis.** Irradiation of ethyl acetate solution of anisole and ethyl chloroacetate in the presence of $ZnCl_2$ gave ethyl *o*-, *m*-, and *p*-methoxyphenylacetates (**3**) (28.6—48%). The similar ethoxycarbonylmethylation in anisole–ethyl acetate (9:1) resulted in higher yields (80—81%) of **3**. The results on the positional and substrate selectivities imply that $ZnCl_2$-participated attacking species would play an important role in the present ethoxycarbonylmethylation.

It has been well known that in the Friedel-Crafts reactions of ordinary carboxylic acids or their esters with aromatic compounds a carboxymethylation or alkoxycarbonylmethylation is difficult. In previous studies,[1] however, we reported that the photochemical ethoxycarbonylmethylation of benzene with ethyl chloroacetate in the presence of metallic halides, such as $SbCl_3$, $AlCl_3$, $ZnCl_2$, and $FeCl_3$, was possible and gave ethyl phenylacetate (2.3—24.4%) as a sole product. We assumed that the reaction might proceed *via* an electrophilic aromatic substitution by such a C-T exciplex as $(MCl^-_{n+1}\cdots\cdots{}^+CH_2CO_2Et)^*$. If this is the case, the similar reaction of anisole, one of electron rich benzenes, could occur more efficiently and show a high positional selectivity. Thus, it was hoped that this reaction would provide greater mechanistic insight into the course of the photochemical ethoxycarbonylmethylation of aromatic compounds with ethyl chloroacetate in the presence of metallic halides. Herein we wish to report the results of our study on the photochemical ethoxycarbonylmethylation of anisole with ethyl chloroacetate in the presence of $ZnCl_2$ and discuss a probable mechanism.

*Reaction Products.* Irradiation of ethyl acetate solution of anisole (**1**) and ethyl chloroacetate (**2**) in the presence of $ZnCl_2$ with an unfiltered low pressure mercury lamp at room temperature for 37 h gave isomeric ethyl methoxyphenylacetates (28.6—48.1% yield) (**3**) accompanied by a trace of diethyl succinate (**4**). As shown in Table 1, addition of $ZnCl_2$ to the reaction significantly increases the yield of ethyl methoxyphenylacetates (**3**), which increases as the concentration of $ZnCl_2$ increases, and at the same time produces noticeable change in the isomer distribution. No photochemical interconversion between each methoxyphenylacetate was observed. The similar ethoxycarbonylmethylation was performed in anisole–ethyl acetate (9 : 1). This resulted in higher yields (80—81%) of methoxyphenylacetates (**3**) and no detection of **4** which eliminates the participation of ethoxycarbonylmethyl radicals. In absence of $ZnCl_2$ **4** was detected, but only in a trace.

Table 1. Photochemical reaction of **1** with **2**

| $[ZnCl_2]$/M | Convn of **2** % | **3** yield[c)] % | Isomer distribution/% *o*- | *m*- | *p*- |
|---|---|---|---|---|---|
| 0[a)] | 48 | 14 | 61.0 | 25.5 | 13.5 |
| 0.09[a)] | 50 | 29 | 66.1 | 19.2 | 14.7 |
| 0.18[a)] | 44 | 38 | 69.2 | 12.5 | 18.3 |
| 0.5[a)] | 38 | 48 | 74.4 | 9.1 | 16.3 |
| 0[b)] | 33 | 38 | 66.1 | 14.6 | 19.3 |
| 0.1[b)] | 51 | 80 | 69.8 | 10.2 | 20.2 |
| 0.5[b)] | 57 | 81 | 70.5 | 11.4 | 18.1 |

a) Used ethyl acetate solutions of 1 M **1** and 0.1 M **2**. b) Used anisol-ethyl acetate (9 : 1) solutions of 0.1 M **2**. c) Based on consumed **2**.

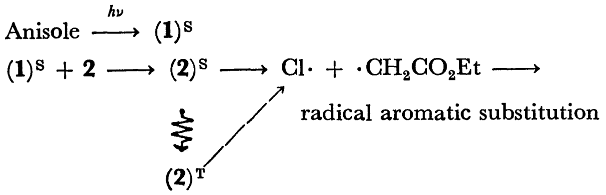
*Positional and Substrate Selectivities.* Data of Table 1 show the effect of $ZnCl_2$ on positional selectivity (as shown with isomer distributions). The isomer distributions did not show any measurable change during irradiation from 3 to 37 h. Thus, the positional selectivity is safely shown with the isomer distribution. Addition of ethyl vinyl ether as a radical scavenger to the reaction without $ZnCl_2$ gave no detectable amounts of **3**. This result, together with the formation of **4** derived from ethoxycarbonylmethyl radicals and results for related reaction,[2] suggests the radical nature of the reaction without $ZnCl_2$. Thus, the relative high proportion of meta isomer in the absence of $ZnCl_2$ may be attributed to a radical substitution by the ethoxycarbonylmethyl radicals.

As shown in Table 2, striking is the significant increase in the values for the Selectivity Factor ($S_f$), as defined by Brown and Smoot,[3] in the reactions with $ZnCl_2$, when compared with those in the absence of $ZnCl_2$. From the $S_f$ values it is possible to say that the reactions in the presence of $ZnCl_2$ proceed *via* competitive radical and non-radical mechanisms, the relative contributions of which depend on the concentration of $ZnCl_2$. The $k_{anisole}/k_{benzene}$ rate ratio ($=k_a/k_b$) in the presence of $ZnCl_2$ is found to be 5.9 from the competitive method. The lower substrate selectivity in the form of low $k_a/k_b$ suggests the reaction to be an electrophilic aromatic substitution involving strongly electrophilic reagent.[4] These results on the positional and substrate selectivities imply that in the non-radical mechanism the carbon atom undergoing attack develops a partial positive charge and may have considerable carbonium ion charactor. Thus, $ZnCl_2$-participated attacking species, as expected previously,[1] would play an important role in the present reaction.

*Fluorescence Quenching of Anisole by Ethyl Chloroacetate.* In order to examine whether the reactions are induced by energy transfer from singlet anisole to **2**, fluorescence quenchings of **1** by **2** were carried out in cyclohexane and cyclohexane–ethyl acetate (1:1) containing $ZnCl_2$. Both solutions showed structureless fluorescence spectra with a maximum at 296 nm. The fluorescences of **1** in cyclohexane and cyclohexane–ethyl acetate containing $ZnCl_2$ are quenched by **2** to give linear Stern-Volmer plots, whose slopes are 18[5] and 7.0 $M^{-1}$ at 13 °C, respectively. The fluorescence quenching with the different efficiency cannot be inferred from the different viscosities of the solutions. The lower efficiency in the presence of $ZnCl_2$ may be attributed to weak interaction between $ZnCl_2$ and **2** in the ground state, although it has been shown that the basicity of ethyl acetate is higher than that of **2**.[6] No fluorescence quenching by only $ZnCl_2$ was observed. Thus, it seems likely that the present reactions are induced by energy transfer from singlet anisole to **2** or that interacting weakly with $ZnCl_2$.[7]

*Reaction Schemes.* Prior to discussing the reaction schemes, the UV spectra of ethyl acetate solutions of anisole in the presence of $ZnCl_2$ were measured. The results show that the spectra do not change by addition of $ZnCl_2$. This implies that there is no interaction between a ground state anisole and $ZnCl_2$ in ethyl acetate. On the basis of the facts mentioned above and before, the possible reaction schemes are outlined as follows:

: without $ZnCl_2$ :



: with $ZnCl_2$ :

$$\underset{\text{S or T}}{2^*} \longrightarrow Cl\cdot + \cdot CH_2CO_2Et \longrightarrow \text{radical substitution}$$

$$(1)^S + \underset{\text{ground state}}{(ZnCl_2\cdots ClCH_2CO_2Et)} \longrightarrow$$

$$\underset{\mathbf{2a}}{(\overset{\delta-}{ZnCl_2}\cdots Cl\cdots \overset{\delta+}{CH_2}CO_2Et)^*}$$

$$\longrightarrow \text{electrophilic aromatic substitution}$$

Thus, in the presence of $ZnCl_2$, an electrophilic aromatic substitution by electronically excited attacking species (**2a**) having considerable carbonium ion charactor may compete with a radical substitution by ethoxycarbonylmethyl radicals. **2a** can be produced by an energy transfer from singlet anisole to **2** interacting weakly with $ZnCl_2$, assuming that the low-lying reactive excited state for **2** is n,$\pi$*.[8]

TABLE 2. $S_f$ IN ETHYL ACETATE

| $[ZnCl_2]$/M | [1]/M | [2]/M | $S_f$[a] |
|---|---|---|---|
| 0 | 0.9 | 0.09 | 0.025 |
| 0.09 | 1.0 | 0.1 | 0.185 |
| 0.18 | 1.0 | 0.1 | 0.476 |
| 0.5 | 1.0 | 0.1 | 0.560 |

a) Calculated from the isomer distribution (Table 1).[3]

## Experimental

*Materials.* Ethyl chloroacetate (**2**), bp 142—143 °C, and authentic diethyl succinate, bp 108—108.5 °C/19 Torr, were prepared as previously described.[1a] Authentic ethyl *p*-methoxyphenylacetate was prepared by the conventional esterification of *p*-methoxyphenylacetic acid: bp 136—139 °C/9.5 Torr. *p*-Methoxyphenylacetic acid, mp 85—86 °C (lit, 84; 87 °C[9]) was prepared by hydrolysis of *p*-methoxybenzyl cyanide obtained by cyanation of *p*-methoxybenzyl chloride. Authentic ethyl *o*- and *m*-methoxyphenylacetates were similarly prepared: ethyl *o*-methoxyphenylacetate, bp 137 °C/14 Torr; ethyl *m*-methoxyphenylacetate, bp 135—138 °C/7 Torr. The *o*- and *m*-methoxybenzyl chlorides were prepared by crossed Cannizzaro reaction between the corresponding anisaldehydes and formaldehyde followed by chlorination with hydrochloric acid.

*Irradiation for Analytical Purposes.* The irradiations were conducted using a Halos 30 W low-pressure mercury lamp without filter. The solutions (5 mL) outlined in Table 1 were placed in 12 mm o.d. quartz tubes, and these were capped with polyethylene-stopples after flushing with nitrogen for about 5 min, then irradiated at 13—23 °C for 37 h. After irradiation, analysis of the reaction mixtures was performed by means of GC.

*Fluorescence Quenching of **1**.* A stock solution of **1** in cyclohexane was prepared and varying amounts of **2** were added to aliquots of the stock: [**1**] = 30 mM, [**2**] = 3.8—30 mM. Five solutions were used for the quenching experiment. The fluorescence spectra were recorded at about 13 °C and the relative intensities ($I_0/I$) at 296 nm in the absence and presence of **2** were plotted with concentration of **2**. A linear Stern-Volmer plot was obtained. Similarly, fluorescence quenching of **1** by **2** containing $ZnCl_2$ (molar ratio = 1:1) was carried out in cyclohexane–ethyl acetate (1:1).

### References

1) (a) Y. Ogata, T. Itoh, and Y. Izawa, *Bull. Chem. Soc. Jpn.*, **42**, 794 (1969); (b) Y. Izawa, T. Ishihara, and Y. Ogata, *Tetrahedron*, **28**, 211 (1972).

2) (a) O. Yonemitsu and S. Naruto, *Tetrahedron Lett.*, **1969**, 2387; (b) Y. Ogata, E. Hayashi, and H. Kato, *Bull. Chem. Soc. Jpn.*, **51**, 3657 (1978).

3) H. C. Brown and C. R. Smoot, *J. Am. Chem. Soc.*, **78**, 6255 (1956).

4) G. A. Olah, S. Kobayashi, and M. Tashiro, *J. Am. Chem. Soc.*, **94**, 7448 (1972), and references cited therein.

5) Assuming that the quenching is diffusion-controlled, from the slope (18 $M^{-1}$) $\tau_f$ is estimated to be $3.4\times10^{-9}$ s (lit, $8.3\times10^{-9}$ s: I. B. Berlman, "Handbook of Fluorescence Spectra of Aromatic Molecules," 2nd ed, Academic Press, New York (1971), p. 139).

6) D. G. Lee and M. H. Sadar, *J. Am. Chem. Soc.*, **96**, 2862 (1974).

7) Alternatively, although the fluorescence quenching by an exciplex formation might be considered, the obserbed positional and substrate selectivities could not be explained by a pathway *via* the exciplex.

8) It has been reported that the reactive excited state is n,$\pi$* triplet state for some organic esters: see, J. A. Bartrop and J. D. Coyle, *J. Chem. Soc.*, *B*, **1971**, 251; A. A. Scala, J. P. Colangelo, G. E. Hussey, and W. T. Stolle, *J. Am. Chem. Soc.*, **96**, 4069 (1974), and references cited therein.

9) "Handbook of Tables for Organic Compound Identification," The Chemical Rubber, Cleveland, Ohio (1967), p. 196.