Supplementary Material Available: Atom positional parameters, bond lengths, and angles for compound **5** (3 pages). Ordering information is given on any current masthead page.


Intramolecular Nucleophilic Participation. 12. Solvolysis of o-(Carbophenoxy)benzhydryl Bromide in 2,2,2-Trifluoroethanol–Benzene Mixtures

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Evidence has been presented in earlier publications[1] that the solvolysis of o-(carbophenoxy)benzhydryl bromide (1)
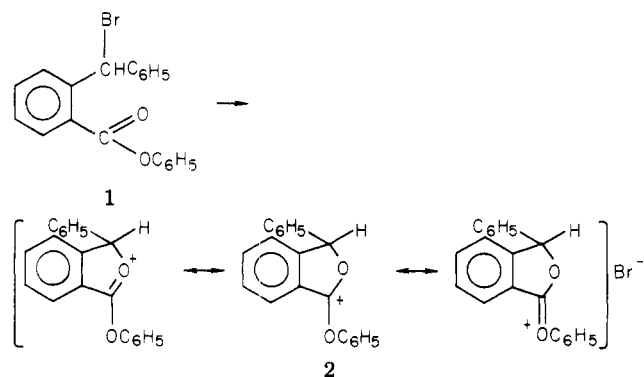

in nucleophilic media is subject to anchimeric assistance by the carbophenoxy group. The reaction is presumed to proceed by way of a cationic (or ion pair) intermediate (2) in which a nonbonding electron pair of the carbonyl oxygen of the ortho substituent is shared with carbon at the reaction center. The product isolated from the reaction in aqueous acetone or in acetic acid is 3-phenylphthalide.

Recent studies of the products and kinetics of the reaction of 1 in 2,2,2-trifluoroethanol (TFE)–benzene mixtures in the presence of 2,6-lutidine have provided further evidence of the involvement of the carbophenoxy group as an internal nucleophile in the solvolytic process. At room temperature the immediate product of reaction in TFE–benzene is the ortho ester **3**. The yield of the
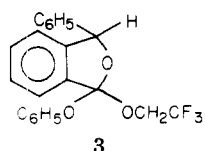

product **3** is by no means quantitative since it is converted

relatively rapidly in the medium to the ortho ester **4**, very
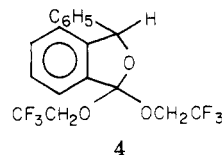
likely by a process involving acid catalysis by lutidinium ion or trifluoroethanol. Compound **4** has been recovered only in small quantity and not in highly pure form, since apparently it decomposes readily to form 3-phenylphthalide. The trapping of the cationic intermediate **2** by solvent with the production of ortho ester calls to mind the experiments of Winstein and Buckles,[2] who isolated the ortho ester **5** (cis isomer) as the product of ethanolysis
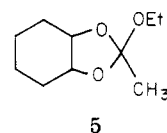
of *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate in absolute ethanol under acid-free conditions. The recovery of **5** as the solvolysis product strongly supported the view that the cation **6** (cis) is formed as a solvolysis intermediate through participation of the acetoxy group as a nucleophile.
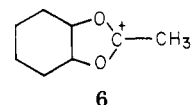
Because of the high reactivity of 1 in TFE–benzene mixtures it has not proved feasible to carry out an extensive investigation of the kinetics of its solvolysis. The results of the limited number of rate measurements which have been made do, however, suggest that the *o*-carbophenoxy group provides extensive anchimeric assistance, considerably more than occurs during hydrolysis[1a] and acetolysis[1b] of 1. As in earlier work[1b] the solvolysis rate of 1 has been compared with the solvolysis rates of *p*-(carbophenoxy)benzhydryl bromide and the *o*- and *p*-bromobenzhydryl bromides. The k_{ortho}/k_{para} rate ratios for reaction of the bromobenzhydryl bromides in TFE–benzene at 10.6 °C in the presence of 2,6-lutidine are 0.091 (20% TFE) and 0.099 (40% TFE); that is, the ortho isomer is less reactive than the para when the ortho substituent, in this case Br, is nonparticipating. The corresponding rate constant ratios, k_{ortho}/k_{para}, for the (carbophenoxy)benzhydryl bromides at 10.6 °C are approximately 3200 (20% TFE) and 3100 (40% TFE).

The very high rate constant ratios, k_{ortho}/k_{para}, for the carbophenoxy compounds in TFE–benzene are supportive of the generally accepted belief that anchimeric assistance by an internal nucleophile (in this case *o*-COOC$_6$H$_5$) should be increasingly reflected in the solvolysis rate as the medium nucleophilicity decreases (trifluoroethanol is considered to be closely comparable in nucleophilicity to formic acid).[3] The possibility cannot be excluded, however, that the solvolysis of the para isomer is more subject to return than is that of the ortho isomer. If this is the case, k_{ortho}/k_{para} ratios are correspondingly inflated, and the extent of anchimeric assistance by the ortho substituent, as measured by those ratios, is overstated.[4]

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(2) S. Winstein and R. E. Buckles, *J. Am. Chem. Soc.*, **65**, 613 (1943).
(3) (a) J. L. Fry, C. J. Lancelot, L. K. M. Lam, J. M. Harris, R. C. Bingham, D. J. Raber, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **92**, 2538 (1970); (b) M. D. Bentley and J. A. Lacadie, *Tetrahedron Lett.*, 741 (1971).

Experimental Section

Materials. The sources and methods of preparation and purification of the benzhydryl bromides and solvents are described in earlier publications.[1,4]

Products of Solvolysis of *o*-(Carbophenoxy)benzhydryl Bromide. A solution of 2.5 g of *o*-(carbophenoxy)benzhydryl bromide in 25 mL of benzene was cooled to 10.6 °C and added to a stirred, cooled solution (10.6 °C) containing 40 mL of 2,2,2-trifluoroethanol, 135 mL of benzene, and 1 mL of 2,6-lutidine. After 1700 s (about 7 half-lives) the stirring was stopped, and 100 mL of the solution of products was removed and mixed with 75 mL of benzene. The benzene layer was extracted several times with 50-mL portions of water and dried over sodium sulfate. The benzene was removed under reduced pressure and the residue dissolved in 40 mL of mixed hexanes. The decolorized hexane solution was stored at –20 °C for 2 days. The white crystals which collected during this time (0.72 g, 0.001 93 mol, 55% yield) were identified as the ortho ester **3**: mp 66–67 °C; NMR (CDCl$_3$) δ 7.25 (m, 14 H, aromatic), 6.15 (s, 1 H, C(3)H), 4.25 (q, 2 H, *J* = 9 Hz, CF$_3$CH$_2$); IR (mineral oil) negligible absorption, 1650–1800 cm^{-1}. Anal. Calcd for C$_{22}$H$_{17}$O$_3$F$_3$: C, 68.39; H, 4.43. Found: C, 68.54; H, 4.33.

The ortho ester **4** was isolated from the products of reaction of *o*-(carbophenoxy)benzhydryl bromide in a medium composed of 67 vol % of trifluoroethanol and 33 vol % of benzene containing a molar excess of 2,6-lutidine (with respect to the starting bromide). After 4 h the products of reaction were isolated by essentially the same procedure as that described above for the isolation of ortho ester **3**. Crystals of the ortho ester **4** were obtained as the major component of a mixture of two visually distinctive types of crystals. The mixture was separated by hand, and the least contaminated portions of the major component were recrystallized from mixed hexanes to yield a white crystalline sample of **4** (mp 42–46 °C) which, though not analytically pure, had the appropriate NMR spectrum: (CDCl$_3$) δ 7.35 (m, 9 H, aromatic), 6.21 (s, 1 H, C(3)H), 4.00 (4 H, m, (CF$_3$CH$_2$)$_2$); IR (mineral oil) negligible absorption, 1650–1800 cm^{-1}. The material obtained from recrystallization of the minor fraction of the product mixture was identified (melting point and mixture melting point) as 3-phenylphthalide. Attempts to obtain the ortho ester **4** in more highly purified form were unsuccessful, presumably owing to its instability.

Rate Studies. The procedures used in the preparation of reaction mixtures and in the analysis of rate samples were similar to those reported previously.[1a,1b] Since the reactions were conducted at a temperature of 10.6 °C, the pipets used in removing samples for analysis from the reaction mixtures were wrapped with glass wool and their tips were enlarged to reduce transfer time. Individual rate samples were transferred to a mixture of crushed ice and acetone and titrated with standard sodium hydroxide solution to the bromthymol blue end point. The recorded volume percentages of benzene and TFE in the rate mixtures are based on the relative volumes of the pure solutions in the solvent mixtures. All reactions were followed to 75% of completion. The reported rate constants were found to be independent of the 2,6-lutidine concentration of the medium. It was noted that in the absence of a sufficient quantity of lutidine to prevent accumulation of HBr during the course of reaction, the solvolyses of *o*- and *p*-(carbophenoxy)benzhydryl bromides do not proceed to completion. The initial concentrations of the organic bromides in the rate mixtures were of the order of 0.02–0.05 M and those of 2,6-lutidine ranged from 0.050 to 0.1 M. The rate constants reported were calculated on the assumption that the reactions obey the rate law given in eq 1. The average values of *k*, based

$$-\mathrm{d}[\mathrm{RBr}]/\mathrm{d}t = k[\mathrm{RBr}] \tag{1}$$

on the results of several rate runs at varying initial concentrations of reactants, are listed as follows (the organic reactant is C$_6$H$_5$CH(Br)C$_6$H$_4$X).

Reactions in 20% TFE: X = *o*-COOC$_6$H$_5$, *k*(10.6 °C) = 3.47 × 10^{-3} s^{-1}; X = *p*-COOC$_6$H$_5$, *k*(10.6 °C) = 0.109 × 10^{-5} s^{-1}; X =

o-Br, *k*(10.6 °C) = 0.226 × 10^{-5} s^{-1}; X = *p*-Br, *k*(10.6 °C) = 2.48 × 10^{-5} s^{-1}.

Reaction in 40% TFE: X = *o*-COOC$_6$H$_5$, *k*(10.6 °C) = 18.7 × 10^{-3} s^{-1}; X = *p*-COOC$_6$H$_5$, *k*(10.6 °C) = 0.60 × 10^{-5} s^{-1}; X = *o*-Br, *k*(10.6 °C) = 2.64 × 10^{-5} s^{-1}; X = *p*-Br, *k*(10.6 °C) = 26.8 × 10^{-5} s^{-1}.

Registry No. 1, 972-99-6; 3, 72283-23-9; 4, 72283-24-0; phenyl 4-[(bromophenyl)methyl]benzoic acid, 973-72-8; 1-bromo-2-[(bromophenyl)methyl]benzene, 29787-98-2; 1-bromo-4-[(bromophenyl)methyl]benzene, 18066-89-2.

A Simple and Mild Method for the Removal of the N^{Im}-Tosyl Protecting Group

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The *p*-toluenesulfonyl (tosyl) group is an attractive group for the protection of the imidazole residue in histidine and histidine derivatives.[1-3] It is easily introduced[3,4] and is stable under various reaction conditions. Moreover, it lowers the basicity of the imidazole nucleus in contrast to, for instance, the benzyl protecting group which enhances the basicity. This is advantageous if one works with histidine derivatives which are prone to base-induced racemization.[5]

Up until now only one reagent, viz., 1-hydroxybenzotriazole, has been mentioned which removes the tosyl group under mild conditions.[3] The reagents commonly used are strong base, sodium in liquid ammonia, or hydrogen fluoride.[3] In particular, the latter compound is dangerous and requires special equipment for its handling. These severe reaction conditions might be a drawback for the use of the tosyl group in routine protections of the imidazole moiety.

We wish to report that the N^{Im}-tosyl group can be removed easily and very mildly by using carboxylic anhydrides and pyridine. Three acid anhydrides were tested, i.e., acetic anhydride, acetic formic anhydride, and trifluoroacetic anhydride (Table I). From these reagents the latter one appears to be the most active and can be used even without pyridine. However, for most standard deprotections acetic anhydride with 2 vol % of pyridine will do. The general applicability of the method is demonstrated on six compounds, including two polymers, which contain imidazole residues in their side chains (Table II).

Removal of the tosyl group probably involves an initial acylation of the imidazole nucleus as depicted in Scheme I. In several cases the salt of acyl intermediate **2** and *p*-toluenesulfonic acid could be detected by TLC and NMR. The latter acid presumably originates from decomposition of acetic *p*-toluenesulfonic anhydride, which is formed simultaneously with **2**, by traces of acetic acid or water in the reaction mixture.

Usually, an N^{Im}-tosyl group is introduced by *p*-toluenesulfonyl chloride and base under Schotten–Bau-

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(4) (a) D. M. Chauncey, Jr., L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **96**, 1850 (1974); (b) S. S. Ball, L. J. Andrews, and R. M. Keefer, *J. Org. Chem.*, **44**, 525 (1979).

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(3) T. Fujii and S. Sakakibara, *Bull. Chem. Soc. Jpn.*, **47**, 3146 (1974).
(4) E. Wünsch in "Methoden der Organischen Chemie (Houben-Weyl)", E. Müller, Ed., George Thieme Verlag, Stuttgart, 1974, Vol 15/1, p 223.
(5) For instance, see: J. H. Jones and W. I. Ramage, *J. Chem. Soc., Chem. Commun.*, 472 (1978).