

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, 0.00193 mol, 55% yield) were identified as the ortho ester 3: mp 66-67 °C; NMR (CDCl₃) δ 7.25 (m, 14 H, aromatic), 6.15 (s, 1 H, C(3)H), 4.25 (q, 2 H, *J* = 9 Hz, CF₃CH₂); IR (mineral oil) negligible absorption, 1650-1800 cm⁻¹. Anal. Calcd for C₂₂H₁₇O₃F₃: 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: (CDCl₃) δ 7.35 (m, 9 H, aromatic), 6.21 (s, 1 H, C(3)H), 4.00 (4 H, m, (CF₃CH₂)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

$$-d[\text{RBr}]/dt = k[\text{RBr}] \quad (1)$$

on the results of several rate runs at varying initial concentrations of reactants, are listed as follows (the organic reactant is C₆H₅CH(Br)C₆H₄X).

Reactions in 20% TFE: X = *o*-COOC₆H₅, *k*(10.6 °C) = 3.47 × 10⁻³ s⁻¹; X = *p*-COOC₆H₅, *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*-COOC₆H₅, *k*(10.6 °C) = 18.7 × 10⁻³ s⁻¹; X = *p*-COOC₆H₅, *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-

(1) S. Sakakibara and T. Fujii, *Bull. Chem. Soc. Jpn.*, **42**, 1466 (1969).

(2) T. Fujii and S. Sakakibara, *Bull. Chem. Soc. Jpn.*, **43**, 3954 (1970).

(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).

(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).

Table I. Detosylation of N^α -Benzoyl- N^{Im} -tosyl-L-histidine Methyl Ester Carboxylic Anhydrides and Pyridine^a

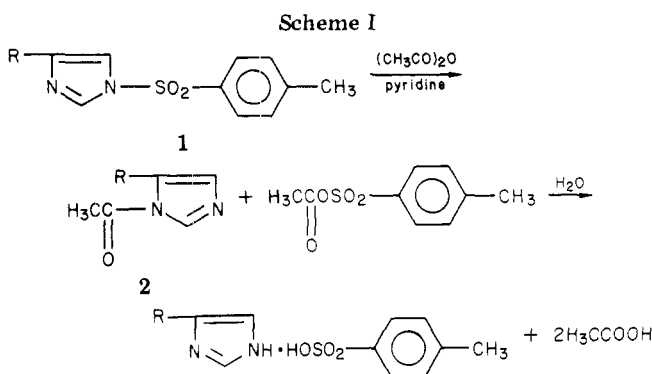
acid anhydride	reactn time, h ^b	acid anhydride	reactn time, h ^b
(CH ₃ CO) ₂ O	3.5 (c)	(CF ₃ CO) ₂ O ^d	0.33 (1)
CH ₃ COOCHO	3 (c)		

^a 1.5 vol %. ^b Reaction time for complete conversion; reaction time for detosylation by carboxylic anhydrides without pyridine is placed in parentheses. ^c After 3 days only a small conversion was observed. ^d For solubility reasons 25 vol % of chloroform was added.

Table II. Removal of the N^{Im} -Tosyl Protecting Group by Acetic Anhydride and Pyridine^a

compound 1 ^b	reactn time, h ^c
a, tosylimidazole	5
b, Bz-His(Tos)-OMe	3.5
c, Im(Tos)CH ₂ CH ₂ NHCHO	1.5
d, CHO-Phe-His(Tos)-OMe	1.5
e, [Im(Tos)CH ₂ CH ₂ N=C<] _n	16 ^d
f, [L,L-Im(Tos)CH ₂ CH(COOCH ₃)-NHCOCH(CH ₃)N=C<] _n	16 ^d

^a 2 vol % unless otherwise indicated. ^b Im = 4-imidazolyl; other abbreviations are according to IUPAC-IUB nomenclature rules; cf. ref 10. ^c Reaction time for complete conversion. Isolated yields are 95–100%. ^d 50 vol % of pyridine was used.



mann conditions.⁴ We have found it very convenient to use 1 equiv of *p*-toluenesulfonyl chloride and solid sodium carbonate in acetonitrile or chloroform-methanol as a solvent. Yields are high (over 90%) and workup is extremely simple.

Experimental Section

Acetic anhydride and trifluoroacetic anhydride were commercial products of analytical grade quality and were used without further purification. Acetic formic anhydride was synthesized according to the literature.⁶ Pyridine (analytical grade) was distilled from KOH before use. TLC was performed on silica gel (Merck F 254

plate) by using chloroform-methanol (9:1, v/v) as the eluent.

Compounds **1a** and **1b** were prepared from imidazole and N^α -benzoyl-L-histidine methyl ester,⁷ respectively. The synthesis of compounds **1c** and **1e** has been published in an earlier paper.⁸ That of compounds **1d** and **1f** will be described elsewhere.⁹

A typical procedure for the introduction and removal of the N^{Im} -tosyl group will be given.

N^α -Benzoyl- N^{Im} -tosyl-L-histidine Methyl Ester (1b). A 5.00-g (18.3 mmol) amount of N^α -benzoyl-L-histidine methyl ester [mp 158.5–159.5 °C; $[\alpha]_{\text{D}}^{20}$ -30.3° (c 2, MeOH)] was dissolved in 25 mL of chloroform and 5 mL of methanol. To this solution was added 5 g of anhydrous sodium carbonate followed by a solution of 3.50 g (18.3 mmol) of *p*-toluenesulfonyl chloride in 10 mL of chloroform, and the mixture was stirred at room temperature. TLC analysis revealed complete conversion after 40 min. The reaction mixture was filtered and concentrated in vacuo to yield 7.80 g (100%) of **1b**, pure according to NMR. Recrystallization from hexane-ethyl acetate afforded a sample which had the following: mp 111–112 °C; $[\alpha]_{\text{D}}^{25}$ +37.2° (c 0.95, CHCl₃); IR (KBr) 1745 (COOCH₃), 1640 (NHCO), 1370 and 1170 cm⁻¹ (SO₂); ¹H NMR (CDCl₃) δ 8.00 and 7.15 (2 s, 2 H, imidazole), 7.75 and 7.25 (2 d, 4 H, tosyl), 7.75 and 7.45 (2 m, 5 H, benzoyl), 7.30 (partly masked, 1 H, NH), 4.95 (t, 1 H, CH), 3.65 (s, 3 H, OCH₃), 3.15 (d, 2 H, CH₂), 2.40 (s, 3 H, CH₃). Anal. Calcd for C₂₁H₂₁N₃O₅S·0.50H₂O: C, 57.80; H, 5.08; N, 9.63; O, 20.16; S, 7.34. Found: C, 57.9; H, 5.0; N, 9.6; O, 20.1; S, 7.3. Apparently, the sample has absorbed 0.50 mol of water of crystallization/mol of compound.

Detosylation of N^α -Benzoyl- N^{Im} -tosyl-L-histidine Methyl Ester. A 2.50-g (5.9 mmol) amount of compound **1b** was dissolved in 25 mL of acetic anhydride and 0.5 mL of pyridine and stirred at room temperature. The progress of the reaction was followed by TLC. When all the starting material (*R_f* 0.66) was consumed (3.5 h), the mixture was concentrated under reduced pressure and the residue stirred with 50 mL of methanol for 1 h. After evaporation of the methanol and methyl acetate, water was added and the pH adjusted to about 8 with solid sodium carbonate. The aqueous layer was extracted five times with 50 mL of chloroform. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to give almost pure detosylated product, identical with an authentic sample: yield 1.60 g (100%); mp 157–158 °C (from methanol-water) (lit.⁶ mp 159 °C); $[\alpha]_{\text{D}}^{21}$ -30.1° (c 1.5, MeOH); IR (KBr) 3300–2700 (unprotected imidazole), 1735 (COOCH₃), 1635 cm⁻¹ (NHCO), and absence of tosyl; ¹H NMR (CD₃OD) δ 7.60 and 6.85 (2 s, 2 H, imidazole), 7.85 and 7.50 (2 m, 5 H, benzoyl), 4.90 (t, 1 H, CH), 3.70 (s, 3 H, OCH₃), 3.20 (d, 2 H, CH₂). Anal. Calcd for C₁₄H₁₅N₃O: C, 61.35; H, 5.53; N, 15.38. Found: C, 61.6; H, 5.6; N, 15.3.

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Registry No. **1a**, 2232-08-8; **1b**, 72318-53-7; **1b**, detosylated product, 3005-62-7; **1c**, 66398-00-3; **1d**, 72317-96-5; **1e**, 66396-61-0; **1f**, 72332-26-4; *p*-toluenesulfonyl chloride, 98-59-9.

(7) H. Bauer, E. Adams, and H. Tabor, *Biochem. Prep.*, **4**, 46 (1955).

(8) J. M. van der Eijk, R. J. M. Nolte, and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **97**, 46 (1978).

(9) J. M. van der Eijk, R. J. M. Nolte, and W. Drenth, to be submitted for publication.

(10) IUPAC-IUB commission on biochemical nomenclature, *J. Biol. Chem.*, **247**, 977 (1972).

(6) I. Muramatsu, M. Murakami, T. Yoneda, and A. Hagitani, *Bull. Chem. Soc. Jpn.*, **38**, 244 (1965).