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**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 added 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), 4.00 (4 H, m, (CF₂Br)₂); IR (mineral oil) negligible absorption, 1650-1800 cm⁻¹. Anal. Calcd for C₂₂H₁₂O₃F₂: 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 distinct 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, (CF₂Br)₂); IR (mineral oil) negligible absorption, 1650-1800 cm⁻¹. Anal. Calcd for C₂₃H₁₄O₃F₃: C, 68.14; H, 4.33. Found: C, 68.26; H, 4.33.

**A Simple and Mild Method for the Removal of the N¹⁰m-Tosyl Protecting Group**

Jan M. van der Eijk, Roeland J. M. Nolte,* and Jan W. Zwikker

Department of Organic Chemistry of the University, Croesestraat 79, 3522 AD Utrecht, The Netherlands


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 introduced4 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.

Up until now only one reagent, viz., 1-hydroxybenzotriazole, has been mentioned which removes the tosyl group under mild conditions.5 The reagents commonly used are strong base, sodium in liquid ammonia, or hydrogen fluoride.6 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 N¹⁰m-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 N¹⁰m-tosyl group is introduced by p-toluenesulfonyl chloride and base under Schotten-Bau-
Table I. Detosylation of \( N^\text{N'-Benzoyl-N'^\text{Im'-tosyl-L-histidine Methyl Ester} \) Carboxylic Anhydrides and Pyridine\( ^d \)

<table>
<thead>
<tr>
<th>Acid anhydride</th>
<th>Reactn time, h(^b )</th>
<th>Acid anhydride</th>
<th>Reactn time, h(^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CH(_2)CO(_2))(_2)O</td>
<td>3.5 (c)</td>
<td>(CF(_3)CO(_2))(_2)O</td>
<td>0.33 (1)</td>
</tr>
<tr>
<td>CH(_2)COOCOO</td>
<td>3 (c)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) 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\(^\text{Im'}\)-Tosyl Protecting Group by Acetic Anhydride and Pyridine\(^d \)

<table>
<thead>
<tr>
<th>Compound 1(^b )</th>
<th>Reactn time, h(^c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>a, tosylimidazole</td>
<td>5</td>
</tr>
<tr>
<td>b, Bz-His(Tos)-O-Me</td>
<td>3.5</td>
</tr>
<tr>
<td>c, Im(Tos)CH(_2)CH(_2)N=CH</td>
<td>1.5</td>
</tr>
<tr>
<td>e, [Im(Tos)CH(_2)CH(_2)N=C]</td>
<td>16(^d )</td>
</tr>
</tbody>
</table>

\(^a\) 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.

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. 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 \( N^\text{N'-benzoyl-N'^\text{Im'-tosyl-L-histidine methyl ester} \) respectively. The synthesis of compounds 1e and 1e has been published in an earlier paper. That of compounds 1d and 1f will be described elsewhere.

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

**Benzoyl-\( N^\text{Im}-\)tosyl-L-histidine Methyl Ester (1a).** A 5.00-g (18.3 mmol) amount of \( N^\text{N'-benzoyl-N'^\text{Im'-tosyl-L-histidine methyl ester} \) [mp 158.5–159.5 °C; \([\alpha]_D^{20} -30.3^\circ \) (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–ethanol acetate afforded a sample which had the following: mp 111–112 °C; \([\alpha]_D^{20} +37.2^\circ \) (c 0.95, CHCl\(_3\)); IR (KBr) 1745 (COOCH\(_3\)), 1640 (C=O, 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, N=), 4.95 (t, 1 H, CH), 3.65 (s, 3 H, OCH\(_3\)), 3.15 (d, 2 H, CH\(_2\)), 2.40 (s, 3 H, CH\(_3\)).

Scheme I

![Scheme I](image)

**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. Pyridine (analytical grade) was distilled from KOH before use. TLC was performed on silica gel (Merck F 254...