



Functionalization of carboxylic anhydrides at α -carbon with hypervalent iodine reagents: one-pot conversion of anhydrides to 2-sulfonyloxycarboxylate esters

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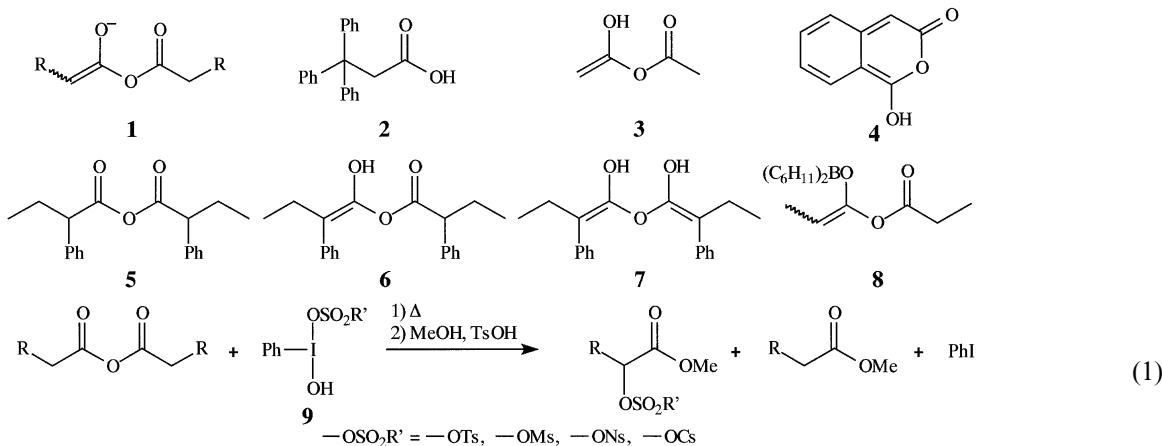
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Abstract—The treatment of carboxylic anhydrides with iodine(III) sulfonate reagents at ca. 100°C and esterification of the reaction mixtures with MeOH/TsOH·H₂O affords 2-sulfonyloxycarboxylate esters. This is consistent with enolic behavior in the anhydrides. © 2001 Elsevier Science Ltd. All rights reserved.

Except for the Perkin reaction,¹ believed to involve enolates, **1**, of carboxylic anhydrides,² little is known about the enolic behavior and α -carbon reactivity of this class of acid derivatives. Literature examples of thermal and acid-catalyzed anhydride enolizations are rare. The production of 3,3,3-triphenylpropanoic acid (**2**) from trityl alcohol and aqueous HBF₄ in acetic anhydride has been reported and attributed to capture of the trityl cation by the enol **3**.³ However, efforts to extend this reaction to propionic and succinic anhydrides were unsuccessful. The treatment of homophthalic anhydride with various dienophiles in aromatic solvents (100–200°C) gives Diels–Alder adducts that spontaneously lose carbon dioxide and afford polycyclic phenols.⁴ Such reactions are presumably initiated by the enol **4**, due to its *o*-xylylene substructure. The most direct evidence for anhydride enolization is provided by studies of 2-phenylbutyric anhydride (**5**). This includes racemization of optically active **5** during vacuum distillation⁵ and NMR observation of mono- and bis-enols, **6** and **7**, when the

distillate from racemic **5** was collected at low temperature and taken up in CCl₄.⁶ The conversion of propionic anhydride to enolborinate **8** with dicyclohexylchloroborane and triethylamine has also been reported.⁷

We now report that carboxylic anhydrides undergo direct oxysulfonylation at α -carbon when they are heated in excess with [hydroxy(sulfonyloxy)iodo]arenes (**9**) at ca. 100°C (Eq. (1)). Treatment of the reaction mixtures with MeOH/TsOH·H₂O affords 2-sulfonyloxycarboxylate esters. Since reported conversions of carbonyl compounds to α -sulfonyloxy derivatives with λ^3 -iodanes require enolizable substrates (ketones, β -dicarbonyl compounds)⁸ or enol derivatives (silyl enol ethers, silyl ketene acetals),⁹ one objective of this study was to explore the enolic behavior of carboxylic anhydrides. The alcoholysis procedure was included to facilitate isolation of clean sulfonyloxy products and provide an alternate route to a class of compounds recently employed to synthetic advantage by Hoffman and co-workers.¹⁰



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In a typical experiment, a two-phase mixture of crystalline [hydroxy(tosyloxy)iodo]benzene (HTIB, 5.0 mmol) and butyric anhydride (24 mmol) was stirred and heated to ca. 100°C, during which time the mixture became homogeneous. After 20 min at 100–105°C, the solution was allowed to cool to 60°C. Methanol (25 mL) and *p*-TsOH·H₂O (0.2 g) were introduced and the solution was heated under reflux for 4 hours and cooled to room temperature. After addition of CH₂Cl₂, extraction with H₂O and concentration of the organic layer, the residual oil was chromatographed on silica gel (20% EtOAc in hexanes) to give methyl 2-tosyloxybutyrate in 61% yield.


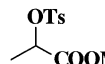
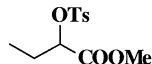
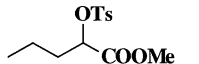
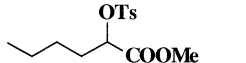
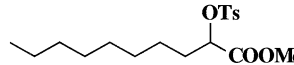
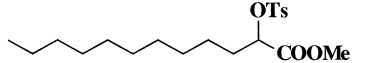
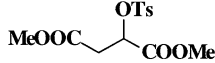
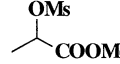
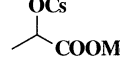
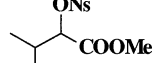
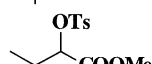

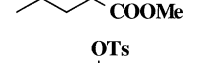
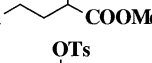
The preparation of 2-sulfonyloxycarboxylate esters by this one-pot procedure is general for a variety of anhydride structures and can also be effected with congeners of HTIB, including the mesyloxy (OMs), nosyloxy (ONs), and (+)-10-camphorsulfonyloxy (OCs) analogs.

The results are presented in Table 1. The 2-sulfonyloxycarboxylate esters were characterized by NMR (¹H, ¹³C), IR, and elemental (C, H) analysis.

The oxytosylation of linear anhydrides with HTIB, ranging in size from acetic to hexanoic, gave methyl 2-tosyloxycarboxylates in isolated yields of 56 to 73% and showed no obvious trend in efficiency. However, with long-chain anhydrides (decanoic and dodecanoic), the yields of 2-tosyloxycarboxylates (41%, 23%) dropped significantly. Among the sulfonyloxycarboxylates prepared from propionic anhydride, the camphor-sulfonate and mesylate derivatives were isolated in comparable yields to the tosylate analog.

The efficiency of anhydride functionalization with HTIB is sensitive to chain-branching in the anhydrides. Thus, while hexanoic anhydride gave a 64% yield of methyl 2-tosyloxyhexanoate, 4-methylpentanoic anhy-

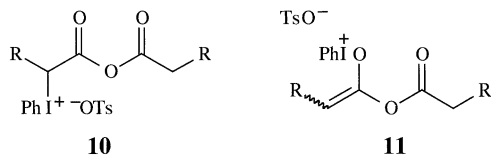
Table 1. Isolated yields of 2-sulfonyloxycarboxylate esters from carboxylic anhydrides with [hydroxy(sulfonyloxy)iodo]arenes

PhI(OH)OSO ₂ R' (mmol)	Anhydride (mmol)	Product	Yield %
5.00	26		66
5.00	25		73
5.00	24		61
5.00	25		56
2.50	12.5		64
1.00	5.4		41
2.50	11.4		23
3.00	15		30
3.00	16		66
3.00	15		62
4.00	20		22
4.00	20		20
3.00	15		41
4.00	20		39
2.00	10		0

dride (γ -branching) gave a 41% yield and 3-methylbutanoic anhydride (β -branching) gave a 20% yield of the corresponding products. 3,3-Dimethylbutanoic anhydride failed to give a 2-tosyloxycarboxylate ester with HTIB. 2-Methylpropanoic anhydride (α -branching) also gave no tosylate derivative with HTIB; in this case methyl methacrylate was produced and isolated as the dibromo adduct in 9% yield.

An attempt to oxytosylate succinic anhydride (melt, ca. 135°C) with HTIB was unsuccessful. However, when the intermolecular anhydride of methyl hydrogen succinate was treated sequentially with HTIB and MeOH/TsOH, dimethyl 2-tosyloxysuccinate was isolated in 30.5% yield.

Based on earlier studies of the oxysulfonylation of ketones, β -dicarbonyl compounds, and silyl enol ethers with iodine(III) sulfonate reagents,^{8,9} the oxytosylation of anhydrides at α -carbon with HTIB is consistent with enolic behavior in the anhydrides and the intermediate formation of 2-phenyliodonio- and/or *O*-phenyliodonio tosylates, **10** and **11**. S_N2 or S_N2' displacement of iodobenzene by the tosylate ion in such intermediates would afford 2-tosyloxyalkanoic anhydrides.



HTIB undergoes competing decomposition reactions in carboxylic anhydrides at the temperatures employed for oxytosylation. For example, although 3,3-dimethylbutanoic anhydride gave no tosylate derivative with HTIB, the iodane was completely reduced after 30 min at 94–95°C, the yield of iodobenzene (GC determination) being 95%. NMR analysis of the reaction mixture revealed no obvious products of anhydride oxidation. In another experiment, HTIB (2.0 mmol) was heated with propionic anhydride (10.0 mmol) for 20 min at 94–95°C. At the end of this time, no oxidant remained (i.e. negative KI test) and the yield of iodobenzene was found to be 94%, or 21% higher than the yield of the ester reported in Table 1. A more complete discussion of the scope, limitations, and mechanisms of anhydride

reactions with hypervalent iodine reagents will be presented in a full report.

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