Tetrahedron Vol. 49, No 8, pp. 1535-1540, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Carboxylic Sulfonic Mixed Anhydrides: General Utility and Application to the Synthesis of Ceftazidime

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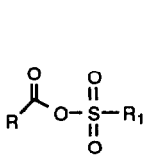
(*Received in USA* 2 *December* 1992)

Abstract: A high-yielding acylation process which utilizes a mixed anhydride of the type $RCO_2SO_2CH_3$ for the synthesis of the cephalosporin ceftazidime is detailed. The mixed anhydride is conveniently prepared by addition of methanesulfonyl chloride to the triethylammonium salt of the acid **2a**. Although known for some time, these anhydrides have not been used often in acylations. This lack of general utility is explained by side reactions, especially formation of the carboxylic symmetric anhydride in sterically unhindered systems.

Mixed anhydrides of carboxylic and sulfonic acids, **1**, have been known for several decades. They have been prepared from the acyl chloride by reaction with sulfonic acids,[1] silver sulfonates,[2] and by exchange with trifluoroacetyl methanesulfonate.[3] Methods for the presumed in situ generation of **1** from the carboxylic acid and p-toluenesulfonyl chloride,[4] benzenesulfonyl chloride,[5] and mesitylsulfonyl chloride[6] have been reported in the context of its use as an acylating agent. More recently, methods for the preparation of esters[7] and symmetric carboxylic anhydrides[8] in which the carboxylic acid is treated with triethylamine and methanesulfonyl chloride have been reported.



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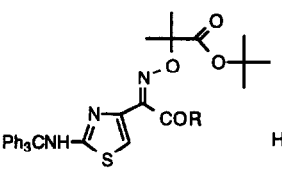
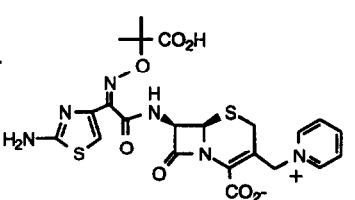


2a: R=OH
2b: R=SO_2Me



Ceftazidime

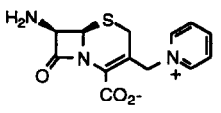
In addition to their use as precursors to esters,[9] symmetric anhydrides, and peptides,[4] these mixed anhydrides have been used for the acylation of aromatic compounds,[10] cleavage of ethers,[11] and preparation of symmetric sulfonic anhydrides through disproportionation.[1] Although a cursory reading of these references might imply widespread utility of these anhydrides, their actual use has been sparse. The present work details the first successful application of a mixed carboxylic-sulfonic anhydride to the synthesis of a commercially important product and a re-examination of the formation and side reactions of simple mixed anhydrides which serves to explain their limited utility for the activation of many carboxylic acids.

RESULTS AND DISCUSSION

The present study relates to the acylation sequence in the synthesis of ceftazidime, a third-generation injectable cephalosporin antibiotic. Two methods for activation of the acid **2a** have been reported. The first, formation of the active ester with 2-mercaptobenzothiazole, suffers from the added expense of manufacture of this ester and removal of the thiol from the product.[12] The second is the preparation of the acyl chloride by reaction of **2a** with phosphorus pentachloride. This approach suffers from the need to separate the

phosphorus oxychloride from the acid chloride, a task accomplished by either crystallization and filtration[13] or by selective hydrolysis of the $POCl_3$ in the presence of the water-sensitive acid chloride.[12]

In contrast, the mixed anhydride, **2b**, is readily prepared within minutes by the addition of triethylamine and methanesulfonyl chloride to the acid **2a**. It shows no degradation over the course of several hours at 0 °C, and may be used directly in solution without removal of by-products. The preferred method of performing this reaction is to add about 1.4 equivalents of triethylamine to a slurry of **2a** in methylene chloride at about -10 °C. This produces a homogeneous solution of the triethylammonium salt of **2a** with sufficient residual triethylamine to produce sulfene[14] upon subsequent addition of about 1.3 equivalents of methanesulfonyl chloride, also at about -10 °C. The formation of **2b** under these conditions is rapid and exothermic. The yield, as determined by HPLC analysis of an aliquot quenched with aniline, is 96 to 98%. Treatment of this reaction mixture with ethanol gives the known ester[12] in high yield without added base or catalysts such as 4-dimethylaminopyridine (DMAP) as used in earlier work.[7] More usefully, the mixed anhydride solution was combined with either a slurry of the amine **3a**, and a base in dimethylacetamide, or a solution of the trimethylsilylated amine, **3b**, in methylene chloride. Rapid acylation occurred in either case to afford the product, **4**, in an in situ yield of about 92% based on HPLC analysis. The known method of isolation of **4** as its dimethylacetamide solvate was used.[12]



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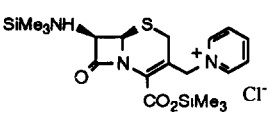

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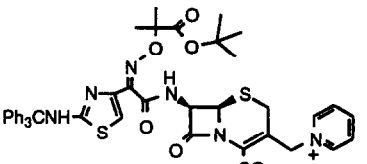

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The production of **2b** is remarkably tolerant of variations in reaction conditions. Acceptable yields of **2b** from **2a** were achieved in dimethylacetamide, ethyl acetate, toluene, acetonitrile, and tetrahydrofuran in addition to methylene chloride. The latter solvent is preferred due to the high solubility of the triethylammonium salt of **2a** in this solvent. Temperatures between -30 and +10 °C for the addition of methanesulfonyl chloride were acceptable. However, slow addition of the methanesulfonyl chloride (over 20 minutes) depressed the yields of **2b** to 80 to 90%. This yield depression is due to formation of the symmetric anhydride.

A second side reaction was identified as the formation of the diethylamide of **2a** from dealkylation of triethylamine; this process was inconsequential when small excesses of triethylamine were used. The minimum amounts of triethylamine and methanesulfonyl chloride which resulted in consistent yields of **2b** in excess of 96% were 1.4 and 1.3 equivalents respectively. Amounts of either reagent up to 2.0 equivalent were not detrimental.

Proof of the structure of **2b** comes from many sources. The solution of **2b** obtained as described has been analyzed by ^1H and ^{13}C NMR and shown to be different than the acid chloride prepared with PCl_5. As mentioned, **2b** reacts with ethanol to give the known ester, aniline to give the anilide, water to regenerate **2a**, and the triethylammonium salt of **2a** to give the symmetric anhydride. Compound **2b** hydrolyzes slowly enough to be visible on a reverse-phase HPLC column but cannot be quantified in this manner. Quantitation of this and all mixed anhydrides reported here occurred in a stepwise fashion; injection of unquenched samples allowed for quantitation of the symmetric anhydride and unreacted acid. Derivatization with aniline and/or an alcohol allowed for quantitation of the mixed anhydride after correction for the amount of anilide or ester originating from the symmetric anhydride and/or acid chloride. By careful addition of ether to solutions of **2b** in methylene chloride, crystalline mixed anhydride was obtained. This material was stable enough to dry and store at ambient temperature.

Given the success with mixed anhydride **2b**, the utility of this method to the activation of other acids was investigated. Initial experiments with benzoic acid indicated that either methanesulfonyl chloride or methanesulfonic anhydride could be used. Use of weak bases such as N-methylmorpholine or the use of arylsulfonyl chlorides instead of alkylsulfonyl chlorides led to significantly higher yields of benzoic anhydride at the expense of the mixed anhydride, presumably due to a change in mechanism away from sulfene formation. Unlike **2b**, methanesulfonyl benzoate was found to react with the byproduct triethylammonium chloride under the reaction conditions. The rate of this bimolecular reaction to give benzoyl chloride was determined by in situ infared spectroscopy to be 1.6×10^{-5} L mole^{-1} s^{-1} at -12 °C for an initial concentration of 0.25 M benzoic acid in methylene chloride.

Results for a variety of carboxylic acids are shown in Table 1. The general experimental procedure consisted of dissolution of the acid in methylene chloride, cooling to about 0 °C, addition of the base, and then addition of the sulfonyl chloride. After reaction times between 10 and 60 minutes, the products were identified and quantitated by the methods mentioned above. All results are an average of at least two experiments.

Table 1. O-Sulfonation of Carboxylic Acids with Methanesulfonyl Chloride/Triethylamine

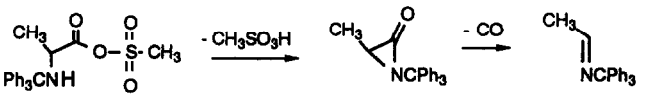
	Product Distribution (% Yield)		
Starting RCO_2H	RCO_2SO_2Me	RCOCl	$(RCO)_2O$
2a	97	0	2
$PhCO_2H$	90	0[a]	10
CBZ-Ala	20	-	80
$PhCH_2CO_2H$	< 5	0	> 85
$(CH_3)_3CCO_2H$	35	54	5
$(CH_3)_2CHCO_2H$	< 2	87	11
$CH_3CH_2CO_2H$	< 2	66	31
CH_3CO_2H	< 2	2	84

[a]Benzoyl chloride is not initially present but is slowly produced; see text.

It is apparent from these results that aliphatic carboxylic acids generally give significant amounts of symmetric anhydride during the production of the mixed anhydrides. This observation may explain the previous researchers' use of DMAP to increase acylation yields.[7] Rapid amidation or even esterification occurs with all of the mixed anhydrides (and acid chlorides) studied here without DMAP. The substrate which produces little symmetric anhydride is pivalic acid, which gives nearly 90% yield of activated materials for acylation. Thus, a large steric component governs the ratio of mixed anhydride to symmetric anhydride. This is not unexpected since symmetric anhydride formation requires reaction of both carboxylate components whereas the high reactivity of sulfene should minimize the importance of the size of the carboxylate during formation of the mixed anhydride. The excellent yield of **2b** from **2a** is thus rationalized by noting the similarity of its electronic structure to benzoic acid (diminished nucleophilicity of the carboxylate due to delocalization) and its large steric bulk due to the Z configuration of the alpha-alkyloxime moiety. Production of acid chlorides from **1** and triethylammonium chloride is also faster for the aliphatic carboxylates than for benzoic acid and **2b**. Although not shown here, the activation of acids which are similar to **2a**, such as other alpha-oximino-alpha-heterocyclic containing materials, to produce other clinically important antibiotics such as cefpodoxime and cefodizime, should be possible under similar conditions.

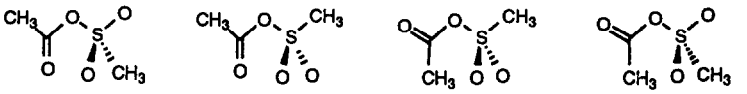
The case of phenylacetic acid requires special note. The literature reports a yield of 73% of ethyl phenylacetate by the reaction of the acid with two equivalents of triethylamine and one equivalent of methanesulfonyl chloride followed by reaction with ethanol and DMAP at 0° for 6 h.[7] An attempt to repeat this reaction gave an in situ yield of only 36%. When the DMAP was omitted, no ethyl ester was obtained. Low-temperature ^1H NMR monitoring indicated that the only observable product of the sulfonation reaction was the symmetric anhydride, not the mixed anhydride. The mixed anhydride was prepared by the thermal reaction of phenylacetyl chloride and methanesulfonic acid.[1] Treatment of aliquots from this reaction with ethanol showed that yields of ethyl phenylacetate of 81 to 85% were possible (without addition of DMAP).

The low yield of the mixed anhydride of CBZ-alanine is consistent with earlier work with p-toluenesulfonyl chloride in which yields of dipeptides of only about 50% were realized.[4] When this activated amino acid was treated with valine methyl ester and N-methylmorpholine, a 62% yield of CBZ-Ala-Val methyl ester was obtained as determined by HPLC.[15] Due to the large steric component of this reaction, the production of the mixed anhydride of methanesulfonic acid and tritylalanine was investigated. Addition of triethylamine and methanesulfonyl chloride to a solution of tritylalanine[16] in methylene chloride produced a gas and a trace of the symmetric anhydride of tritylalanine. The main product was identified as the imine of tritylamine and acetaldehyde by comparison with the authentic condensation product of these materials. This imine underwent slow aza-aldol condensation to give the imine of tritylamine and crotonaldehyde. The presumed mechanism involves decarbonylation of an alpha-lactam.



CONFORMATIONAL ANALYSIS

Since steric factors play such a key role in determining the yield of the mixed anhydride from the carboxylate and sulfene, a conformational analysis of **1**, R=R_1=CH_3,[17] was performed. The results, summarized in Table 2, show that **1a** and **1b** are predicted to be the most stable of the four possible conformers by both MM2 and AM1 methods. Since more highly functionalized versions of **1** are likely to favor **1a** and **1b** even more than does this simple model, the conformers **1c** and **1d** should not be considered by future researchers unless the carboxylate and sulfonate groups are tethered together. The coincident polarization vectors of the carbonyl and sulfonyl groups in conformer **1b** give it a high dipole moment. It is interesting to speculate that this is responsible, in part, for the high reactivity of these mixed anhydrides.



1a **1b** **1c** **1e**

Table 2. Conformational Analysis of Methanesulfonyl Acetate **1**, R=R_1=CH_3.

Parameter	Method	1a	1b	1c	1d
Relative Energy (Kcal/mol)	MM2	0	1.2	5.8	9.2
Relative Energy (Kcal/mol)	AM1	0	0.9	4.5	5.3
Dipole Moment (Debye)	"	2.9	5.1	2.5	4.7

CONCLUSION

In conclusion, the optimized mixed carboxylic-sulfonic anhydride method of acyl activation gave excellent yields of a protected version of the clinically and commercially important antibiotic ceftazidime. The method is rapid, utilizes inexpensive materials, and gives side products which are readily separated from the acylated product. Acid chloride and symmetric anhydride formation were the major side reactions of this activation method. Symmetric anhydride formation is the most serious limitation to the general utility of the method for sterically unencumbered alkyl carboxylic acids.

EXPERIMENTAL

General. ^1H NMR data were recorded at 300 MHz and ^{13}C NMR at 75 MHz on a Bruker AC300. All experiments were performed under an atmosphere of nitrogen in glassware which was not specially dried. Reagents were commercial grade and were used as received; solvents were spectroscopic grade and were used as received. High performance liquid chromatography was performed on a Spectra Physics 8700XR/4270 system. The aqueous phase was prepared by addition of 0.4% H_3PO_4 (by volume) to filtered water followed by triethylamine to achieve a pH of 3.0 to 3.5. Detection was by UV. Gas chromatography was performed on a Perkin-Elmer 5890 with flame ionization detection and a helium flow which was split 1:100 for the DB1701 capillary column. Pivalic, isobutyric, propionic, and acetic acid systems were analyzed by this method with commercially available materials as standards. Amino acids and their esters and CBZ-Ala-Val methyl ester were purchased from Sigma Chem. Co.; all other reagents were purchased from Aldrich Chem. Co.

Molecular mechanics (MM2) were performed on Macromodel^R 3.0[18] on a VAX cluster with the PRCG minimizer. Semi-empirical (AM1) calculations were performed on the same hardware using SYBYL^R/NITRO^R, version 5.4, as a graphic interface.[19] MOPAC^R version 5.0 was used and augmented with published sulfur parameters utilizing the keyword EXTERNAL=.[20] Full optimization of all geometric parameters and the default convergence criteria were used.

(6R,7R)-7-[(Z)-2-(2-triphenylmethylaminothiazol-4-yl)-2-(2-*t*-butoxycarbonyl-prop-2-oxyimino)acetamido]-3-(1-pyridiniummethyl)ceph-3-em-4-carboxylate, 4. A slurry of 8.31 g (14.6 mmol) of (Z)-2-(2-*t*-butoxycarbonylprop-2-oxyimino)-2-(2-triphenylmethylaminothiazol-4-yl)acetic acid, **2a**, in 50 mL of CH_2Cl_2 was cooled to 0 °C and 3.6 mL of Et_3N (25.9 mmol) was added. The resulting homogeneous solution was cooled to -10 °C and 1.70 mL of MsCl (21.9 mmol) dissolved in 5 mL of CH_2Cl_2 was added. In a separate flask was mixed 15.1 g of bis(trimethylsilyl)urea (72 mmol), 5.0 g of (6R, 7R)-7-amino-3-(1-pyridiniummethyl)ceph-3-em-4-carboxylic acid dihydrochloride dihydrate (12 mmol)[12], and 50 mL of CH_2Cl_2 . After 2.5 h, this slurry was cooled to 0° C and the mixed anhydride solution was added rapidly. After 45 min in an ice bath, 85 mL of water was added followed by Et_3N to raise the pH to 6.5. Dimethylacetamide, 25 mL, was added; the lower layer was separated and the aqueous phase extracted with 10 mL of CH_2Cl_2. The combined organic layers were evaporated in vacuo. To this concentrate was added 10 mL each of dimethylacetamide and ethyl acetate. The solution was seeded and stirred for 45 min. A solution of 15 mL of dimethylacetamide and 50 mL of diethyl ether was added over 45 min. After a 30 min stir at ambient temperature and a 45 min stir in an ice bath, the product was isolated by filtration, washed with dimethylacetamide and ethyl acetate. The product was dried in vacuo at 30 °C to yield 9.06 g; it is a solvate containing 14% by weight of a mixture of dimethylacetamide and ethyl acetate so that the isolated yield was 77% of theory.

For HPLC monitoring, a 25 cm Zorbax C8 column was eluted at 1.25 mL/min with 40% aqueous and 60% THF. Detection was by UV at 254 or 270 nm. Durene could be used as an internal standard. Compound **2a** eluted at 4 min, the anilide at 10 min, and the symmetric anhydride at 20 min.

Isolation of **2b**. The preparation of **2b** was repeated as above. Five minutes after addition of the MsCl, 20 mL of diethyl ether was added over 15 min. The slurry was filtered after 2 min to remove triethylamine hydrochloride. The filtrate was stirred at -10 °C for 3 h. The slurry was filtered and the product washed with a 1:1 mixture of methylene chloride and ether. It was dried at 30 °C in vacuo for 1 h to give 3.1 g (36%) of a white solid, mp 120-4 (dec.); FAB MS: m/z = 243 (trityl), 650 (M+H); HRMS: found 650.1983, calc. 650.1995; IR ($CHCl_3$) 1794, 1731, 1530, 1386, 1103, 961 cm^{-1}; ^1H NMR ($CDCl_3$, all singlets) 7.4 (15H), 6.75 (1H), 3.42 (3H), 1.55 (6H), 1.45 (9H); ^{13}C NMR ($CDCl_3$, tr=trityl, th=thiazole) 171.4 (th), 167.6, 156.2, 143.7, 142.8 (tr), 139.0, 128.8 (tr), 127.8 (tr), 127.1 (tr), 109.0 (th), 83.3, 81.0, 71.8, 40.3 (SO_2Me), 27.5, 23.3.

Anilide of 2a. Acid **2a** (7.54 g, 13.2 mmol) was slurried in 40 mL of methylene chloride and 3.1 mL of dimethylacetamide, cooled to -10 °C and phosgene was added (5.1 mL of a 3.6 M solution in methylene chloride). After stirring 1.5 h at this temperature, 4.8 mL of aniline (53 mmol) was added over 5 min. The mixture was stirred for 1 h and 50 mL of water was added. The pH was raised to 5 with triethylamine and the layers separated. The solution was evaporated to a viscous oil and 50 mL of methanol was added. After stirring for 2h, the product was filtered, rinsed with methanol, and dried in vacuo at 40 °C. The yield of white solid was 7.62 g (89%), mp. 182-184 °C. The purity by the above HPLC technique was 98.4%. ^1H NMR ($CDCl_3$) 9.6 (s, 1H), 7.64 (d, J=1.0, 2H), 7.3 (m, 16H), 7.09 (t, J=1.0, 2H), 6.86 (s, 1H), 6.83 (1H, thiazole), 1.57 (s, 6H), 1.49 (s, 9H). ^{13}C NMR ($CDCl_3$) 174.9, 168.0, 160.8, 151.0, 143.1, 138.1, 129.3, 128.9, 128.2, 127.5, 124.1, 119.7, 113.1, 82.4, 71.7, 27.9, 24.0. Anal. Calcd for $C_{38}H_{38}N_4O_4S$: C, 70.56; H, 5.92; N, 8.66; S, 4.96, found: C, 70.45; H, 5.84; N, 8.94; S, 5.06. IR ($CHCl_3$) 1718, 1681, 1601 cm^{-1}. HRMS (FAB, H^+) Calcd 647.2692, found 647.2720.

Methanesulfonyl benzoate. Benzoic acid (1.00 g, 8.2 mmol) and 20 mL of methylene chloride were combined and the solution cooled to -10 °C. Triethylamine (1.45 mL, 10.4 mmol) was added and the solution cooled again to -10 °C. Methanesulfonyl chloride (0.80 mL, 10.3 mmol) was added rapidly and the solution held at 0 °C for various lengths of time while sampling. Chromatography was performed on a 25 cm Supelco LC8-DB column eluted at 1.3 mL/min with 52% aqueous solution (0.3% H_3PO_4 by volume, Et_3N to pH 2.5) and 48% acetonitrile. Detection was by UV at 254 nm. Samples were diluted 1:500 for analysis, unquenched samples with acetonitrile and quenched samples with an acetonitrile solution containing 20% each of aniline and triethylamine. Quantitation was performed against a standard curve generated from commercially available products. When the reaction was performed in CD_3CN, it could be conveniently monitored by ^{13}C NMR. In addition to benzoyl chloride (169 ppm) and benzoic anhydride (164 ppm), resonances were observed for the mixed anhydride at 162, 136, 132, 130, and 40 ppm.

N-CBZ-L-Ala-Val Methyl ester. Utilizing CBZ-L-alanine, 1.4 equiv. of triethylamine, and 1.05 equiv. of methanesulfonyl chloride and the procedure described for benzoic acid, yields of about 80% of the symmetric anhydride and 20% of the ethyl ester when quenched with ethanol (with no loss of symmetric anhydride) were obtained. After 4 h at 0 °C, 1.0 equiv. of valine methyl ester hydrochloride and 2.0 equiv. of N-methylmorpholine were added. After stirring for 30 min. at 0 °C, an in situ yield of 62% of CBZ-Ala-Val methyl ester was obtained. Chromatography was performed on a 25 cm. LC8-DB column with 48% aqueous and 52% acetonitrile as eluent with detection at 215 nm. Retention times for the amino acid, symmetric anhydride, ethyl ester, and dipeptide were 3.1, 8.3, 5.3, and 4.5 minutes, respectively.

N-CBZ-L-Alanine anhydride. N-Carbobenzoxy-L-alanine (2.0 g, 9.0 mmol) was added to 20 mL of methylene chloride. After cooling to 0 °C, 1.37 mL of triethylamine (9.8 mmol) was added. The homogeneous solution was cooled again and 0.36 mL of methanesulfonyl chloride (4.6 mmol) was added. After 20 min, 10 mL of water was added and the pH raised to 7 with sat. sodium bicarbonate solution. The phases were separated and the lower phase washed with 15 mL of chilled water. The solution was dried over sodium sulfate and evaporated to a white solid. The solid was slurried at ambient temperature for 30 min in 25 mL of diethyl ether. After filtration and drying overnight at 40 °C in vacuo, 1.17 g (61%) of a white solid was obtained. The purity by the above HPLC system was >99%. mp. 117-120 °C. ^{1}H NMR (acetone-d_6) 7.3 (m, 10H), 6.9 (d, J=7.3, 2H), 5.09 (s, 4H), 4.37 (pentet, J=7.4, 2H), 1.45 (d, J=7.4, 6H). When the experiment was repeated with racemic CBZ alanine, an additional product was obtained as evidenced by both NMR and HPLC (retention time 5.9 min). Although the isolated anhydride from CBZ-L-alanine did not contain this material, it was present at a level of about 4% before the reslurry in ether, indicating that some racemization occurs with this method.

Acknowledgment. The first experiments with **2b** were performed by Mr. L. J. McShane and the in situ IR experiments were performed by Dr. P. Graham; their contributions are gratefully acknowledged.

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