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AN EXPLANATION FOR THE FAILURE OF AMINOMETHANESULFONIC ACID TO FORM SULFONAMIDES. ACYL CHLORIDE-PROMOTED GENERATION OF α-CARBOXAMIDOALKYLATING ELECTROPHILES.

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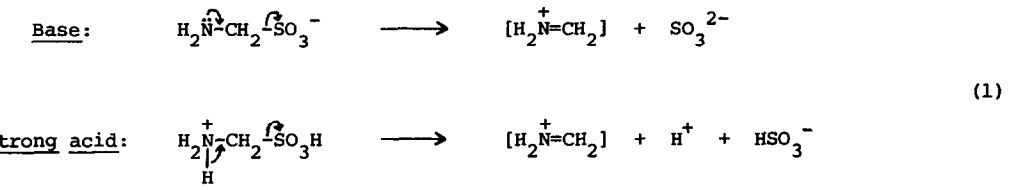
Attempted N,N-dibenzoylation of aminomethanesulfonic acid results in C-S bond cleavage, generating synthetically useful α-benzamidomethylating electrophiles. The importance of this observation in regard to the reported failures to prepare sulfonamide analogs of peptides is discussed.

Sulfonamide analogs of peptides, in which glycine is replaced by $H_2NCH_2SO_3H$ (1), would be very interesting for a variety of reasons, and it is surprising that their preparation has not been reported. Upon failing to achieve the functionalization of 1 according to several frequently employed methods of peptide synthesis, Frankel and Moses[1] concluded that α-aminoalkylsulfonic acids do not form sulfonamides. In this communication we provide an explanation for this failure and report on a novel and perhaps synthetically useful method of generating α-carboxamidoalkylating electrophiles.[2]

Previously understood problems associated with the observed failure of 1 to form sulfonamides included an unusually low nucleophilicity of the sulfonate moiety coupled with an inherent overall instability of the $H_2NCH_2SO_3H$ molecule.[1] It is known that 1 is unstable in basic or acidic aqueous solution, ultimately decomposing to sulfur dioxide and formaldehyde.[1] Upon examination of the plausible mechanisms for C-S bond rupture (eq 1), it appears that the



(1)

molecular disintegration reflects either the availability of an electron pair on nitrogen (in the former case) or an improved sulfonyl-containing leaving group (in the latter case). In support of this notion is the observation that N-acylation of 1 confers base stability to

the molecule.[1]

It appeared plausible that by taking advantage of the stability of N-acyl derivatives of 1, the elusive sulfonamide might be obtainable if sufficient activation of sulfonate could be achieved under mild conditions. We felt that conversion of the sulfonate to a mixed sulfonic anhydride of CF_3SO_3H, which should react with amines in the desired direction,[3] would be possible even for a poorly nucleophilic sulfonate by treating its silver salt with trifyl chloride. The precedent for this approach was established in a model reaction wherein benzylamine was converted to (N-benzyl)methanesulfonamide by a preformed, equimolar mixture of silver methanesulfonate, trifyl chloride, and pyridine in acetonitrile.[4] The observed requirement for pyridine in this reaction suggests that it is necessary to stabilize the sulfonylating electrophiles in the form of Lewis base complexes (eq 2).

$$CH_3SO_3Ag + CF_3SO_2Cl \xrightarrow[AgCl\downarrow]{py} CH_3SO_3^- \; CF_3SO_2py^+ \xrightarrow[-\,py]{slow} [CH_3SO_2OSO_2CF_3]$$

$$\xrightarrow[+\,py]{fast} CF_3SO_3^- \; CH_3SO_2py^+ \xrightarrow{PhCH_2NH_2} CH_3SO_2NHCH_2Ph + CF_3SO_3^- \; pyH^+ \qquad (2)$$

In order to assess the applicability of the above method to aminomethanesulfonic acid, it was first desirable to protect the amino group as an imide. The treatment of 1 with one equivalent of benzoyl chloride (in the presence of an excess of tertiary amine base) gave the monobenzoyl derivative 2, but further treatment did not afford the desired dibenzoyl compound, resulting instead in desulfonation to 3 (eq 3, R_3N = triethylamine and/or pyridine).[5]

$$\underset{1}{H_2NCH_2SO_3H} \quad \text{or} \quad \underset{2}{PhC(=O)NHCH_2SO_3^- \; R_3NH^+} \xrightarrow[CH_3CN]{PhCCl,\ R_3N} \underset{3}{PhC(=O)NHCH_2NR_3^+ \; Cl^-} + (PhC(=O))_2O + SO_2 \qquad (3)$$

The complete conversion of 2 to 3 required two equivalents of benzoyl chloride and generated one equivalent of benzoic anhydride.

The stability of 2 to base precludes this as the cause of the observed C-S bond fission. The fact that benzoyl chloride is the limiting reagent for complete desulfonation suggests that the above reaction proceeds according to eq 4, via a mixed anhydride at sulfonate: the leaving group stability of benzoate helps provide the driving force for desulfonation. Although 2 is stable to base, desulfonation does occur in hot 100% H_2SO_4.[6] The latter can

$$\underset{\underline{2}}{PhCNHCH_2SO_3^-\ R_3NH^+} + PhCCl \longrightarrow \underset{\underline{4}}{[PhCNHCH_2SO_2OCPh]} \xrightarrow[-\ SO_2]{R_3N}$$

$$\underset{\underline{3}}{PhCNHCH_2NR_3^+} + PhCOO^- \xrightarrow{PhCCl} (PhC)_2O \qquad (4)$$

be rationalized in terms of the improved leaving group ability of sulfonate upon protonation or formation of a mixed anhydride of H_2SO_4. Thus it appears that the critical requirement for C-S bond rupture is related to a sufficient activation of sulfonate.

The product of the presently observed desulfonation (3) is well known as a member of one class of synthetically important α-carboxamidomethylating agents.[2] These quaternary salts yield a variety of nucleophilic substitution products and react with active methylene compounds in the presence of base to afford products of alkylation at carbon. That 3 can be generated in essentially quantitative yield from the commercially available 1 in one step may provide a useful alternative to the usual production of 3 from benzamide, formaldehyde, and a tertiary amine hydrochloride.[2] Of greater interest may be the fact that the attempted extension of the conventional synthesis of 3 to the preparation of α-carboxamidoalkylating agents, $R''CNHCHR'NR_3^+$ (R' ≠ H), by substituting higher aldehydes for formaldehyde, fails in all but a few exceptional cases.[2] On the other hand, subjecting the easily prepared α-aminoalkanesulfonic acids,[1] $H_2NCHR'SO_3H$, to the conditions of eq 3 should serve as a general method of producing the desired agents.

Desulfonation is not the only course that reaction may take when 1 or its monoacyl derivatives are treated with electrophilic reagents. In an attempt to see if the monobenzoyl compound 2 was suitable for carrying out the sulfonamide synthesis outlined in eq 2, we treated silver benzamidomethanesulfonate with trifyl chloride in acetonitrile in the presence of pyridine, and later added benzylamine. The desired product 5 was not detected, and if the reaction alternatively followed a course similar to eq 4, the expected product would have

$PhCNHCH_2X$

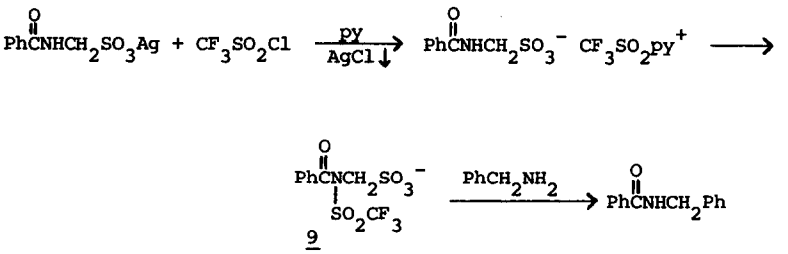
X = SO_2NHCH_2Ph 5

$NHCH_2Ph$ 6

$SO_2OSO_2CF_3$ 7

py^+ 8

been 6, formed ultimately via the intermediates 7 and 8. The major product isolated, however, was N-benzylbenzamide, which arose by a benzoyl group transfer from 9 (eq 5). The triflation



of a secondary amide and transfer of the acyl group to an acceptor nucleophile are both known processes.[7] The divergent course taken by the trifyl chloride reaction (eq 5) compared to the benzoyl chloride reaction (eq 4) is undoubtedly related to the involvement of much more reactive electrophilic species in the former case.

In summary, this work has helped to illuminate the unusual chemical properties of aminomethanesulfonic acid and suggests that any synthetic approach to the desired sulfonamide derivatives which utilizes N-protection of 1 as the initial step, offers little likelihood of success. Since many of the previously attempted syntheses would have theoretically involved mixed anhydrides of one sort or another, analogous to 4 or 7, it is conceivable that the observed failures were not a consequence of an insufficient nucleophilicity of sulfonate, but instead the result of either C-S bond fission in the presumed intermediate anhydride (eq 4) or other side-reactions (e.g., eq 5). In addition, we have uncovered a mild method for generating synthetically useful α-carboxamidoalkylating agents under neutral conditions and from readily available starting materials.

REFERENCES AND NOTES

1) M. Frankel and P. Moses, Tetrahedron, 9, 289 (1960).
2) H. E. Zaugg and W. B. Martin, Organic Reactions, 14, 52 (1965).
3) In analogy with the trifluoroacetic anhydride method of acylation: see E. J. Bourne, M. Stacey, J. C. Tatlow, and R. Worrall, J. Chem. Soc., 2006 (1954) and literature cited.
4) Although we realized only a 60% yield, it was expected that this yield could be improved by appropriate modifications of the reaction conditions.
5) With excess R_3N, the SO_2 is released as a base complex, but in the absence of base, C-S bond rupture still occurs and is accompanied by direct evolution of SO_2 gas.
6) The reactive benzamidomethyl cation generated was found to alkylate benzene: S. Tanimoto, K. Kyo, and R. Oda, Kogya Kagaku Zasshi, 65, 1583 (1962); Chem. Abstr., 59, 505 (1963).
7) J. B. Hendrickson and R. Bergeron, Tetrahedron Lett., 4607 (1973); J. B. Hendrickson, R. Bergeron, A. Giga, and D. Sternbach, J. Am. Chem. Soc., 95, 3412 (1973).

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