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INTRAMOLECULAR SULFONAMIDE-CARBOXAMIDE REARRANGEMENT

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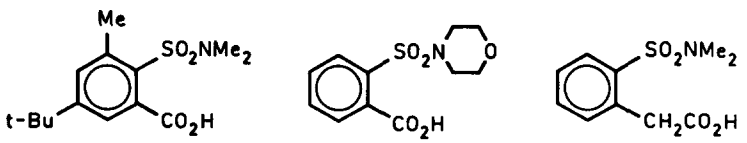
Abstract: Several o-carboxy-N,N-dialkylbenzenesulfonamides rearrange intramolecularly to o-chlorosulfonyl-N,N-dialkylbenzamides upon treatment with an excess of thionyl chloride in an apolar solvent.

During our studies of the intramolecular carboxyl-catalyzed hydrolysis of sulfonamides[1] we found that several o-carboxy-N,N-dialkylbenzenesulfonamides (1) rearrange in high yield[2] to the corresponding o-chlorosulfonyl-N,N-dialkylbenzamides (2) upon treatment with an excess of thionyl chloride in an apolar solvent[3]:

1 2

A similar reaction occurs with $SOBr_2$ instead of $SOCl_2$[4]. The ease of the rearrangement strongly depends on the nature of the substituents at nitrogen in 1 as indicated by half-life periods ($t_{1/2}$)[5] at 25°C. The relative rates follow the sequence of pK_a values of the amine part (HNR_1R_2) in the substrate: 1a, R_1=R_2=Me, pK_a^{am} = 10.73, $t_{1/2}$ = 45 min.; 1b, pK_a^{am} = 10.73, $t_{1/2}$ = 1h.; 1c, R_1=Me, R_2=CH_2Ph, pK_a^{am} = 9.58, $t_{1/2}$ = 3 hs.; 1d, R_1=R_2= allyl, pK_a^{am} = 9.29, $t_{1/2}$ = 12 hs. This

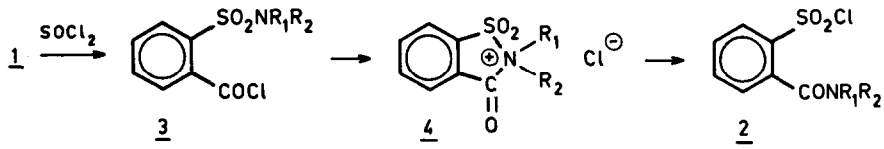


1b 1e 1j

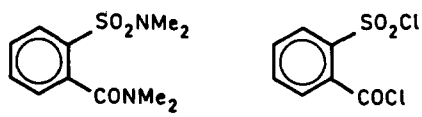
suggests that nucleophilic attack by the sulfonyl nitrogen atom is involved in

the activation process. If the pK_a^{am} falls below ca. 9.0, no rearrangement is observed (1e; 1f, R_1=Me, R_2=p-$CH_3OC_6H_4$; 1g, R_1=Me, R_2=Ph; 1h, R_1=Me, R_2=OMe; 1i, R_1=Me, R_2=p-$NO_2C_6H_4$). In these cases the reaction stops at the stage of the acyl chloride derived from 1 (at 25°C as well as at 60°C). A similar acyl chloride is also the sole product obtained from 1j.

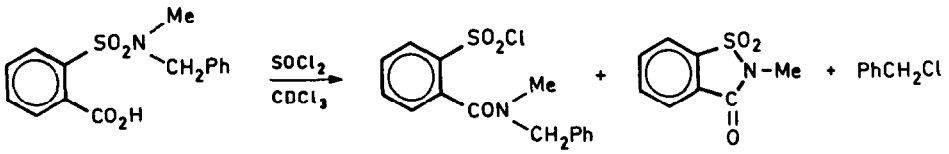
We propose that the rearrangement occurs via the following pathway:



The intramolecular migration of the substituted amino group is supported by the observation that the p-substituted isomer of 1a does not undergo the rearrangement after treatment with 8 equiv. of $SOCl_2$ in $CDCl_3$ for 4 days at 25°C, despite rapid formation of the acyl chloride. Additional evidence for an intramolecular process is provided by the observed pseudo-first-order kinetics of the conversion of 3 into 2 and by the finding that no reaction is observed when a 1:1 mixture of 5[6] and 6[7] is treated with thionyl chloride in dichloromethane for 3 days at 25°C[8]. The rapid and quantitative formation of 3 as an intermediate[9]



is consistent with a change in the NMR spectrum during the first five minutes of the reaction. Subsequent spectral changes indicate rate determining formation of 2 from this intermediate. No signals of the high-energy intermediate 4 were observed. Interestingly, however, the rearrangement of 1c is accompanied by the formation of N-methylsaccharin (7) and benzyl chloride (8) as sideproducts[10]:

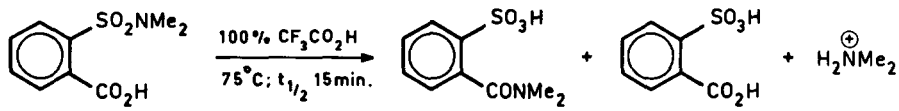


1c 2c. 40% 7. 35% 8. 20%

Nucleophilic attack of the chloride anion on benzylic carbon in intermediate 4 readily accounts for this observation. The preference for nucleophilic attack at benzylic carbon rather than at methyl is well-documented[11,12].

The resistance of 1j to undergo rearrangement (less than 5% after 3 days at 25°C) is in agreement with previous findings for related systems[1] which show that a six-membered ring intermediate is more strained than a five-membered ring analogue.

Finally we note that the rearrangement of 1a does also occur in anhydrous trifluoroacetic acid at 75°C but is then accompanied by the formation of substantial amounts of solvolysis products[13]:



1a 66% 33% 33%

In contrast to the intramolecular carboxyl-catalyzed hydrolysis of sulfonamides[1], this reaction does not proceed via the cyclic mixed anhydride[14]. Again, sulfonamide 1j reacts much slower ($t_{1/2}$ 280 min. at 75°C, 70% rearrangement vs 30% solvolysis).

References and Notes

(1) T. Graafland, W.C. Nieuwpoort, and J.B.F.N. Engberts, J. Am. Chem. Soc. 103, 4490 (1981) and previous papers in this series.

(2) The yields are essentially quantitative, but usually there is some hydrolysis of

2 to the corresponding sulfonic acid during work-up. Side reactions only occur in the case of 1c.

(3) The sulfonamides 1a, 1c, 1d, 1e, and 1h were prepared from methyl (o-chlorosulfonyl)benzoate [I. Remsen and A.R.L. Dohme, Am. Chem. J. 11, 332 (1889)] by treatment with HNR_1R_2 in dichloromethane and subsequent ester hydrolysis in the presence of sodium hydroxide. The sulfonamides 1f, 1g, and 1i have been described [T. Graafland, A. Wagenaar, A.J. Kirby, and J.B.F.N. Engberts, J. Am. Chem. Soc. 101, 6981 (1979)]. Sulfonamide 1b was synthesized from 2,6-dimethyl-4-t-butylbenzenesulfonamide [E.H. Huntress and J.S. Autenrieth, J. Am. Chem. Soc. 63, 3446 (1941), in this paper an incorrect structure is assigned to the sulfonamide] via oxidation to the saccharin derivative, followed by methylation (MeI), hydrolysis (NaOH) to the ester, methylation and again hydrolysis.
Reaction products were characterized by spectroscopic (IR, NMR) and analytical data. Detailed information on the synthesis of the materials described in this paper is available on request.

(4) Reaction rates with $SOBr_2$ are about the same as those with $SOCl_2$, but now solubility problems are encountered during the first stages of the reaction.

(5) Reactions were followed by ^{1}H-NMR spectroscopy using 0.4M solutions of the sulfonamides. About the same $t_{1/2}$ values were found in benzene, dichloromethane, and deuterochloroform. The $t_{1/2}$ values are independent of the thionyl chloride concentration, provided that this reaction component is present in a 4-8 fold excess.

(6) I. Remsen and F.E. Clark, Am. Chem. J. 30, 291 (1903).

(7) D.S. Rozina, L.T. Nesterenko, and Y.I. Vainshtein, Zhur. Obschei. Khim. 28, 2878 (1958).

(8) Compare: G. Schroeter, Angew. Chem. 39, 1460 (1926).

(9) The relative stability of the intermediate suggests that it is the acyl chloride rather than the chlorosulfite; compare: M.F. Ansell in "The Chemistry of Acyl Halides", S. Patai, Ed., Interscience, New York, p. 35 (1972).

(10) The yields of 7 and 8 refer to isolated compounds. Compound 2c was isolated as the corresponding sulfonic acid after crystallization from moist acetone.

(11) J. v. Braun, Justus Liebigs Ann. Chem. 382, 1 (1911).

(12) E.D. Hughes and C.K. Ingold, J. Chem. Soc. 69 (1933).

(13) Concentration of 1a: 0.2M. Yields were determined by NMR spectroscopy.

(14) This anhydride does not react with dimethylamine in 100% CF_3CO_2H at 75°C. Small amounts of water lead to rapid hydrolysis.

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