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PARTICIPATION OF A PERI-HYDROXYL GROUP IN THE TRIFLUOROACETOLYSIS OF NAPHTHALENESULFONAMIDES

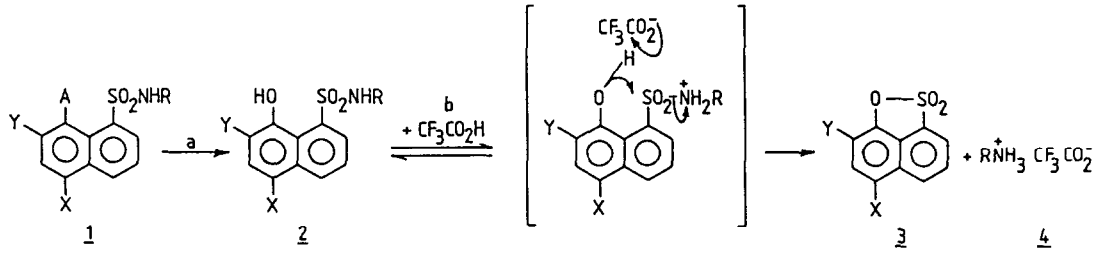
Jean-Paul MAZALEYRAT and Michel WAKSELMAN*

CNRS-CERCOA 2, rue Henry Dunant 94320 THIAIS (France)

Summary : Trifluoroacetolysis of N-alkyl-8-hydroxy-naphthalenesulfonamides generally leads to the corresponding amines and naphthosultones. A model experiment shows that this reaction may be used in a two-step cleavage of sulfonamide protecting groups.

Semi-permanent protection of the ε-amino group of lysine[1], guanidino group of arginine[2], imidazole group of histidine[3] and indolic group of tryptophane[4] by sulfonylation has been recently reported. Introduction of methoxy and/or polyalkyl substituents generally increases the rate of the acidic cleavage of these arenesulfonamides. However, a delicate balance between stability in trifluoroacetic acid (TFA) and ease of cleavage in more acidic medium at the end of the synthesis has to be found so as to selectively cleave the *tert*butoxycarbonyl (Boc) α-amino protecting group at each stage of the chain elongation without removal of the side-chain protecting groups.

We purpose to study a different two-step mechanism of cleavage in which the arenesulfonamide precursor 1 containing a latent hydroxyl group A at the *peri* position would be completely stable in TFA and could selectively lead to a 8-hydroxy-1-naphthalenesulfonamide 2 (step a ; Scheme I). Then participation of the *peri*-hydroxyl group in the trifluoroacetolysis of 2 would give a sultone 3 and amine salt 4 (step b).



1 2 3 4

Scheme I

Participation of alcoholic[5] and carboxylic[6] groups in the acidic hydrolysis of benzenesulfonamides is known. The residence time of interacting functions within a bonding distance is of crucial importance for the rate of intramolecular reactions[7,8] and the *peri*-effect[9] on a naphthalene skeleton could favor the participation of a phenolic group. As model compounds for examination of step b, the sulfonamides 2a-e and 6 have been prepared by aminolysis[11] of the corresponding sultones[12]. Trifluoroacetolysis of these sulfonamides has been followed by UV spectroscopy in neat trifluoroacetic acid at 25°C. In all but one case, the corresponding sultones 3 and amine salts 4 were formed, and nice isosbestic points were observed. However, in the case of the dinitrosulfonamide 2e (X=Y=NO_2), the release of the amine 4 was not accompanied by the formation of sultone 3e, although this sultone was checked to be stable in the reaction conditions, suggesting the occurence of a different mechanism[15].

Excellent *pseudo*-first-order plots were obtained for all kinetics, and the calculated rate constants are reported in Table I.

Table I : Calculated *pseudo*-first-order rate constants for trifluoroacetolysis of the sulfonamides 2 in neat trifluoroacetic acid at 25°C.

Sulfonamide[a]				$10^3 k_{obs}$	$t_{1/2}$
n°	X	Y	R	min^{-1}	min
2a	H	H	bzl	0.3	2160
2b	Ts	H	bzl	1.9	368
2c	Ts	I	bzl	5.5	126
2d	NO_2	H	bzl	5.7	121
2'b	Ts	H	Pr	4.2	164
2'c	Ts	I	Pr	15.8	44
2e	NO_2	NO_2	bzl	14.6[b]	47[b]
6				0[c]	[c]

a) bzl=$CH_2C_6H_5$; Pr=n-C_3H_7 ; Ts=p-$SO_2C_6H_4CH_3$

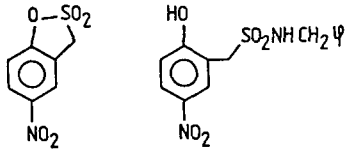
b) The absorption curve of the final product does not correspond to the one of sultone 3e.

c) No reaction after 1 month at 25°C.

From these data, it appears that the rate constants are higher (by a factor of ca.3) for the sulfonamides derived from the more basic n-propylamine, as compared to benzylamine.

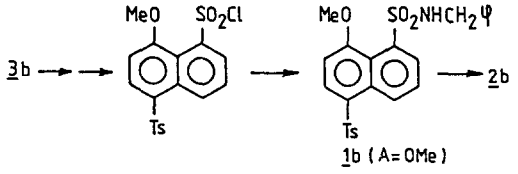
Electron withdrawing groups X=Ts,NO_2 in *para* position of the naphthol ring favor the reaction. Introduction of an iodine atom in *ortho* position also enhances the rate constant by a factor of ca.3, possibly because of a contribution of both electronic and steric effects.

The inertness of N-benzyl-(3-nitro-6-hydroxy-phenyl) methanesulfonamide 6 (Table I), having also a neighbouring phenol grouping, supports the hypothesis that the *peri*-effect is responsible for the reactivity of sulfonamides 2.



5 6

As a model of the first step a of scheme I the cleavage of the methoxysulfonamide 1b (A=OMe) has been studied (scheme II).



Scheme II

This compound was prepared from the corresponding sulfonyl chloride. As expected[16] it was found to be very stable in TFA (no alteration after 4 days at room temperature). The cleavage of the methyl ether group by means of BBr_3[18] gave the hydroxysulfonamide 2b with a 80 % yield.

References and Notes

(1) a) M. Fujino, M. Wakimasu and C. Kitada, J. Chem. Soc. Chem. Comm. 1982, 445.
b) K. Saito, T. Higashijima, T. Miyazawa, M. Wakimasu and M. Fujino, Chem. Pharm. Bull. 1984, 32, 2187.

(2) a) H. Yajima, M. Takeyama, J. Kanaki and K. Mitani, J. Chem. Soc. Chem. Comm. 1978, 482.
b) M. Fujino, M. Wakimasu and C. Kitada, Chem. Pharm. Bull. 1981, 29, 2825.

(3) a) K. Kitagawa, K. Kitade, Y. Kiso, T. Akita, S. Funakoshi, N. Fujii and H. Yajima, J. Chem. Soc. Chem. Comm. 1979, 955. b) M. Wakimasu, C. Kitada and M. Fujino, Chem. Pharm. Bull. 1982, 30, 2766.

(4) N. Fujii, S. Futaki, K. Yasumara and H. Yajima, Chem. Pharm. Bull. 1984, 32, 2660.

(5) T. Graafland, A. Wagenaar, A.J. Kirby and J.B.F.N. Engberts, J. Amer. Chem. Soc. 1979, 101, 6981.

(6) a) A. Wagenaar, A.J. Kirby and J.B.F.N. Engberts, J. Org. Chem. 1984, 49, 3445.
b) H. Watanabe, R.A. Schwartz and C.R. Hauser, J. Chem. Soc. Chem. Comm. 1969, 287.

(7) F.M. Menger, Acc. Chem. Res. 1985, 18, 128.

(8) The participation of an *ortho*-hydroxymethyl group in the acidic hydrolysis of benzenesulfonamides is strongly favored by C-substitution on the methylene (Thorpe Ingold effect)[6].

(9) Typical 1,8-disubstituted naphthalenes that have been examined by X-ray analysis and NMR spectroscopy show a distorsion pattern consistent with a repulsion between the substituents[10]. However, in the case of naphthalenes bearing nucleophilic and carbonyl centers, the bond to the nucleophile is splayed toward the carbonyl[10a,10b].

(10) a) J.D. Dunitz, "X-ray Analysis and the Structure of Organic Molecules" Cornell University Press 1979, p. 373. b) W.B. Schweizer, G. Procter, M. Kaffory and J.D. Dunitz, Helv. Chim. Acta 1978, 61, 2783. c) F. Imashiro, K. Takegoshi, A. Saika, Z. Taira and Y. Asahi, J. Amer. Chem. Soc. 1985, 107, 2341. d) I.I. Schuster and J.D. Roberts, J. Org. Chem. 1980, 45, 284. e) V. Balasubramanian, Chem. Rev. 1966, 66, 567.

(11) E. Ciuffarin, M. Isola and P. Leoni, J. Org. Chem. 1981, 46, 3064.

(12) The sultones 3a, 3b, 3d, 3e and 5 are known[13]. The sultone 3c has been synthesized with a 85 % overall yield by iodation[14] of sulfonamide 2'b and cyclisation.

(13) a) E.T. Kaiser and Kwok-Wing Lo, J. Amer. Chem. Soc. 1969, 91, 4912. b) G. Schetty, Helv. Chim. Acta 1947, 30, 1650. c) F. Acher and M. Wakselman, J. Org. Chem. 1984, 49, 4133.

(14) T. Kometani, D.S. Watt and T. Ji, Tetrahedron Lett. 1985, 26, 2043.

(15) A general base catalysis of the trifluoroacetolysis by the neighbouring but weakly nucleophilic dinitronaphthol group may occur.

(16) The 8-methoxy group is located on a *meta*-like position and is not electron-releasing (σ=0.12[17]).

(17) G.B. Barlin and D.D. Perrin, Quart. Rev. 1966, 20, 75.

(18) Boron tribromide[19] has been used for the cleavage of numerous carbamate, ester and ether protecting groups in peptides without degradation in most cases[20].

(19) M.V. Bhatt and S.V. Kulkarni, Synthesis 1983, 249.

(20) a) A.M. Felix, J. Org. Chem. 1974, 39, 1427. b) J. Pless and W. Bauer, Angew. Chem. Int. Ed. 1973, 12, 147.

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