Facile hydrolytic cleavage of a sulfonamide bond under microwave irradiation

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The hydrolysis of a sulfonamide bond in 25% sulfuric acid under microwave irradiation was completed in 0.5 h.

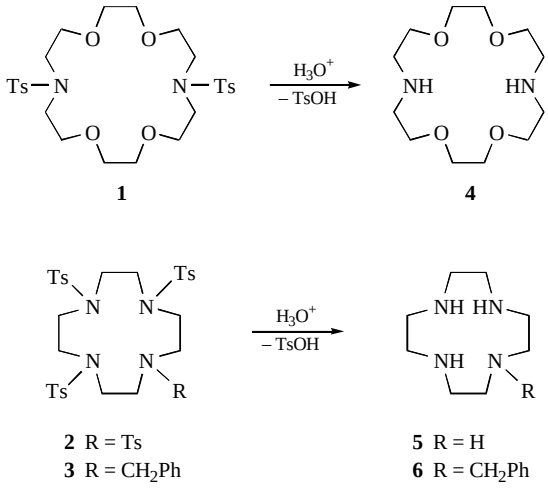
Acid hydrolysis reactions are widely used in organic synthesis. However, severe conditions of hydrolytic cleavage are responsible for undesired side reactions resulting in degradation of starting materials and reaction products. Therefore, it is of particular importance to select mild conditions for the hydrolytic removal of protective groups used in multistage syntheses.

The tosyl (*p*-toluenesulfonyl) group is used as an activator or protector of terminal hydroxyl and amino groups in the Richman–Atkins synthesis of macroheterocyclic compounds.[1] This group exhibits the following advantages: it is easy to introduce into reactant molecules and stable in the course of subsequent reactions. However, the necessity of removing this group under severe conditions is a consequence of its stability.

The removal of protective tosyl groups under mild conditions can facilitate the synthesis, preclude many side reactions, and increase the yields of target compounds. In this case, compounds with a wide variety of functional groups that were unsuitable because of degradation in the course of subsequent severe acid hydrolysis of the sulfonamide bond can be used as the starting materials. Thus, a significantly greater number of macroheterocyclic compounds can be synthesised by the simple and convenient Richman–Atkins method.

It has been found[2–4] that the rate of hydrolysis of organic compounds was dramatically increased under microwave irradiation, and the use of concentrated acids was not necessary in these reactions. We believed that a similar effect will also occur in the hydrolysis of the sulfonamide bond and examined 1,10-ditosyl-1,10-diaza-4,7,13,16-dioxacyclooctadecane **1**, 1,4,7,10-tetratosyl-1,4,7,10-tetraazacyclododecane **2** and 1-benzyl-4,7,10-tritosyl-1,4,7,10-tetraazacyclododecane **3** as examples. Table 1 summarises the reaction conditions and the yields of compounds **4**–**6**.[†,‡] Compounds **4** and **5** were identified by TLC using specially synthesised diaza-18-crown-6[4] and cyclen[5] as the reference samples. Compound **6** was identified by the ^{1}H NMR and mass spectrometry data.

We have found that the rate of hydrolytic cleavage of the sulfonamide bond dramatically increased (by a factor of 100–200) under microwave irradiation. Moreover, the substrate/acid ratios and the concentrations of acids can be considerably decreased resulting in an increase in the yields and purity of the hydrolysis products.



Scheme 1

It has been found[6] that detosylation of **3** with an HBr solution in acetic acid resulted in the removal of the benzyl group along with three tosyl groups. The same result has been obtained with the use of concentrated sulfuric acid (Table 1). Recently, it has been found[5] that compound **6** is formed in 26% yield by treatment of a solution of compound **3** (3.5 g) in 1 l of liquid ammonia with 6 g of sodium metal.

We found that the hydrolysis of **3** with a 25% sulfuric acid solution for 0.5 h under microwave irradiation gives rise to compound **6** in 80% yield (Table 1). Thus, the use of microwave heating significantly shortened the duration of hydrolysis of the N–Tos bond (by a factor of 100 or higher). The reaction was performed in a dilute acid; thus, the amount of strongly acidic waste solutions was significantly decreased.

We believe that the effects observed resulted from a rapid increase in the temperature of the reaction mixture (up to a limiting value of 200 °C, which can be attained in the microwave oven used). Moreover, direct absorption of microwave radiation by the substrate cannot also be ignored. Whittaker and Mingos[3] suggested that this absorption was the cause for significant acceleration of reactions in a microwave field.

† *Typical procedures of commonly used hydrolysis*: a suspension of **1** (1.0 g, 1.75 mmol) in 5.5 ml of 33% HBr solution in glacial acetic acid was kept at 100 °C for 48 h. The solvent was evaporated to dryness; the residue was treated with 10 ml of anhydrous ether, filtered off, washed with 10 ml of anhydrous ether, and treated with 5 ml of a 20% NaOH solution. The aqueous solution was extracted with $CHCl_3$ (5×2 ml), and the extract was dried with anhydrous Na_2SO_4. The solvent was evaporated, and the residue was recrystallised from benzene–heptane. Compound **4** (321 mg) was obtained, mp 115 °C. For **2**: a suspension of **2** (1.0 g, 1.27 mmol) in 5.1 ml of 97% H_2SO_4 was kept at 100 °C for 100 h. After cooling, it was added to 20 ml of anhydrous ether; the precipitate was filtered off, washed with 10 ml of anhydrous ether and treated with 5 ml of 20% NaOH. The solution was extracted with CH_2Cl_2 (5×2 ml), and the extract was dried with Na_2SO_4. The solvent was evaporated, and the residue was recrystallised from heptane. Compound **5** (196 mg) was obtained, mp 111–112 °C. For **3**: a suspension of **3** (1.0 g, 1.38 mmol) in 5.0 ml of 97% H_2SO_4 was kept at 100 °C for 70 h. The subsequent procedure was analogous to that described for compound **2**. The yield of **5** was 178 mg.

‡ *Typical procedures of hydrolysis under microwave irradiation*: a mixture of **1** (1.0 g, 1.75 mmol) and 5 ml of a 25% H_2SO_4 solution was placed in a Teflon autoclave of an MDS-2000 microwave oven (CEM Corporation, USA) and exposed for 0.5 h at 350 W. Next, the pH of the solution was adjusted to 10 with 20% NaOH, and the solution was extracted with $CHCl_3$ (5×2 ml). The extract was dried with Na_2SO_4, and the solvent was evaporated to dryness. Recrystallisation of the residue resulted in 436 mg of **4**. For **2**: 1.0 g (1.27 mmol) of **2** yielded 497 mg of **5** in a manner described above. For **3**: 1.0 g (1.38 mmol) of **3** yielded 289 mg of **6** as colourless oil in a manner described above. ^{1}H NMR spectrum for **6** (D_2O, HCl) δ: 3.2 (m, 16H, $8CH_2$), 4.1 (s, 2H, CH_2Ph), 7.3 (s, 5H, C_6H_5). MS, *m*/*z*: 263 $(M + 1)^+$.

Table 1 Commonly used hydrolysis and hydrolysis under microwave irradiation of compounds **1**–**3**.

Starting materials	Commonly used hydrolysis[a]				Hydrolysis in a microwave field[b]			
	Conditions	Time/h	Product	Yield (%)	Conditions	Time/h	Product	Yield (%)
1	5.5 ml of 33% HBr in AcOH	48	**4**	70	5.0 ml of 25% H_2SO_4	0.5	**4**	95
2	5.1 ml of 97% H_2SO_4	100	**5**	90	5.0 ml of 25% H_2SO_4	0.5	**5**	90
3	5.0 ml of 97% H_2SO_4	70	**5**	75	5.0 ml of 25% H_2SO_4	0.5	**6**	80

[a] See footnote †. [b] See footnote ‡.

References

1 E. J. Richman and T. J. Atkins, *J. Am. Chem. Soc*., 1974, **96**, 2268.
2 R. A. Abramovich, *Org. Prep. Proced. Int*., 1991, **23**, 685.
3 A. G. Whittaker and V. M. P. Mingos, *J. Microwave Power and Electromagnetic Energy*, 1994, **29**, 195.
4 K. D. Raner, C. R. Strauss and R. W. Trainor, *J. Org. Chem*., 1995, **60**, 2456.
5 D. D. Dishino, E. J. Delaney, J. E. Emswiler, E. T. Gaughan, J. S. Prasad, S. K. Srivastava and M. F. Tweedle, *Inorg. Chem*., 1991, **30**, 1265.
6 D. I. Weisblat, B. J. Magerlein and D. R. Myers, *J. Am. Chem. Soc*., 1953, **75**, 3630.

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