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Short Communication

Unusual Hofmann Elimination at Low Temperature. Reaction of 3-Hydroxymethylpyrrolidines with *p*-Toluensulfonyl Chloride

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Summary. *Trans*-2-aryl-3-hydroxymethyl-1-methylpyrrolidines suffer an unusual Hofmann elimination when treated with *p*-toluensulfonyl chloride in basic medium at room temperature.

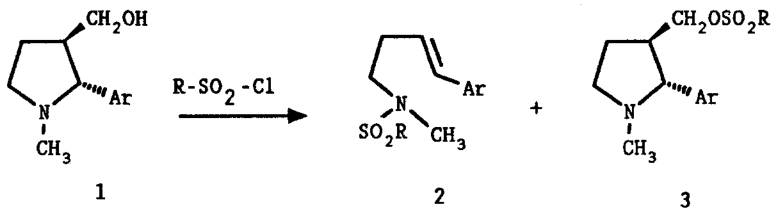
Keywords. Hofmann elimination; Pyrrolidines.

Ungewöhnliche Hofmann-Eliminierung bei niederer Temperatur. Die Reaktion von 3-Hydroxymethylpyrrolidinen mit *p*-Toluolsulfonylchlorid (Kurze Mitt.)

Zusammenfassung. *Trans*-3-hydroxymethylpyrrolidine erleiden in basischem Medium bei Behandlung mit *p*-Toluolsulfonylchlorid eine ungewöhnliche Hofmann-Eliminierung.

Hofmann elimination reactions have been used extensively in synthesis and structural analysis. Beside of the great number of examples of this reaction, the formation of the products obtained under Hofmann elimination conditions can be explained normally by the standard mechanism and very few examples have been reported on abnormal degradations or sideway reactions induced by the presence of other functional groups [1–4]. In the course of a synthetic project of 2-aryl-3-pyrrolidine acetic acid derivatives, we found that in the reaction of *trans*-3-hydroxymethyl-2-(*p*-methoxyphenyl)-1-methylpyrrolidine (**1a**) (Scheme 1) with *p*-toluensulfonyl chloride and sodium hydroxyde in dichloromethane at room temperature, the sulfonamide **2a** was isolated in 62% yield [5] instead of the desired tosylated alcohol 3a. This unexpected result prompted us to study this reaction, since the mechanism of this process could be related to a Hofmann like reaction.

Other pyrrolidine alcohols such as **1b** and **1c** afforded mixtures of the elimination products **2b** (15% yield) and **2c** (3% yield) along with the tosylated derivatives **3b** (22% yield) and **3c** (38% yield).



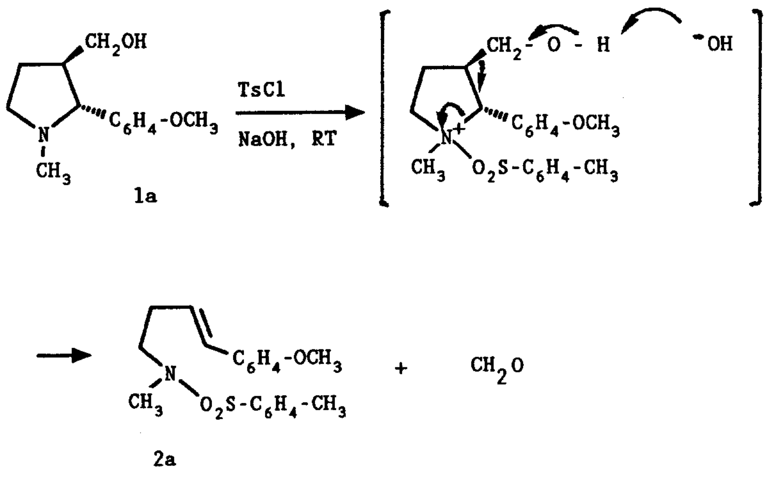
	Ar
a	p-CH_3O-C_6H_4
b	p-CH_3-C_6H_4
c	Ph

R- p-$CH_3C_6H_4$, CH_3

Scheme 1

In order to check the influence of the sulfonyl halide in this process, alcohols **1a–c** were reacted with mesyl chloride, delivering only the corresponding mesylates **3a–c** ($R = CH_3$, 70%, 83%, 55% isolated yields).

The formation of the sulfonamides **2** can be envisaged as a Hofmann elimination reaction (Scheme 2) induced by the attack of the tosylate, that can be considered a soft electrophile, to the pyrrolidine nitrogen atom, followed by the elimination of formaldehyde, instead of a proton as in the case of the classical Hofmann reaction. With Mesyl chloride, a hard electrophile, the corresponding Hofmann elimination products **2** were not detected. As Hofmann elimination reactions need normally high temperatures (120 °C) this first example of an assisted Hofmann elimination at room temperature increases the scope of this process. Further studies with different aryl substituents, other removable groups, electrophiles and reactions with acyclic systems are in progress.



Scheme 2

References and Notes

[1] Kametani T., Kigasawa K., Hiiragi M., Wakisaka K., Uruy, T., Sugi H., Saitoh S., Ishimaru H., Haga S. (1976) Chem. Pharm. Bull. **24**: 1246

[2] Liu J-H., Kovaciv P. (1975) J. Org. Chem. **40**: 1183

[3] Doshi H., Cardis A. B., Crelling J. K., Miller S. I., Dalton D. R., Zacharias D. E., Gluster J. P. (1987) J. Org. Chem. **52**: 2604

[4] Sladkov V. I., Sazonova N. M., Kuleshova L. N., Lindeman S. V., Struchkov Y. T., Suvorov N. N. (1989) Zh. Org. Khim. **25**: 854

[5] Satisfactory elemental analysis was obtained. Spectral data for **3a**: γ_{max} ($CHCl_3$): 1340 cm^{-1} (*Ar*–SO_2–N); ^1H NMR, δ ($CDCl_3$): 2.39 (3 H, s), 2.42 (2 H, q, $J = 7$ Hz), 2.74 (3 H, s), 3.10 (2 H, t, $J = 7$ Hz), 3.78 (3 H, s), 5.99 (1 H, dt $J = 16$ and 7 Hz), 6.34 (1 H, d, $J = 16$ Hz), 6.81 (2 H, d, $J = 9$ Hz), 7.23 (2 H, d, $J = 9$ Hz), 7.27 (2 H, d, $J = 8$ Hz), 6.65 (2 H, d, $J = 8$ Hz); ^{13}C NMR: 21.4 (q), 31.6 (t), 34.8 (q), 49.9 (t), 55.2 (q), 113.8 (d), 123.8 (d), 127.1 (d), 127.3 (d), 129.5 (d), 129.9 (s), 131.5 (d), 134.6 (s), 143.2 (s), 158.9 (s)

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