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Studies on the Chemistry of 1,4-Oxazines, XV [1]: Synthesis of Ethyl 3,4-Dihydro-4-tosyl-2*H*-1,4-benzoxazine-3-carboxylate

Short Communication

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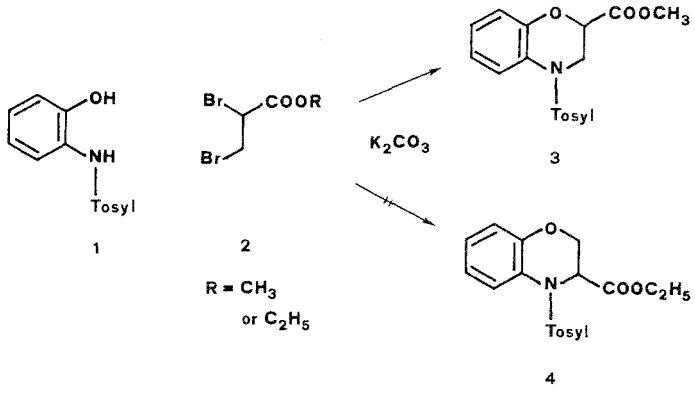
A four step synthesis of ethyl 3,4-dihydro-4-tosyl-2*H*-1,4-benzoxazine-3-carboxylate (**4**) from the acetal **5** is described.

(Keywords: Unambigous synthesis; Ethyl dihydro-1,4-benzoxazine-3-carboxylate)

Studien zur Chemie der 1,4-Oxazine, 15. Mitt. [1]: Synthese des 3,4-Dihydro-4-tosyl-2H-1,4-benzoxazin-3-carbonsäureethylesters (Kurze Mitteilung)

Eine Synthese des 3,4-Dihydro-4-tosyl-2*H*-1,4-benzoxazin-3-carbonsäureethylesters (**4**) über vier Stufen wird, ausgehend vom Acetal **5**, beschrieben.

Scheme 1



Recently we reported [2] that reaction of **1** with the dibromoester **2** leads to the benzoxazine-2-carboxylate **3** instead of the C-3 isomeric compound **4**, as described in Ref. [3] (Scheme 1). Our structural assignment was based on spectroscopic evidence.

In the present study we describe the synthesis of the above-mentioned benzoxazine-3-carboxylate **4** via the corresponding carbonitrile, obtained by the following unambigous synthetic pathway, as elaborated for 4-acyl-3,4-dihydro-2*H*-1,4-benzoxazine-3-carbonitriles [1]:

Treatment of **5** [4] with *p*-toluenesulfonyl chloride gives the N-tosylated acetal **6**, which can be cyclized to **7** by two different methods. Reaction with trimethylsilylcyanide leads to the carbonitrile **8**. *Pinner* reaction and successive hydrolysis of the intermediate imidoate yields **4** (Scheme 2).

Scheme 2

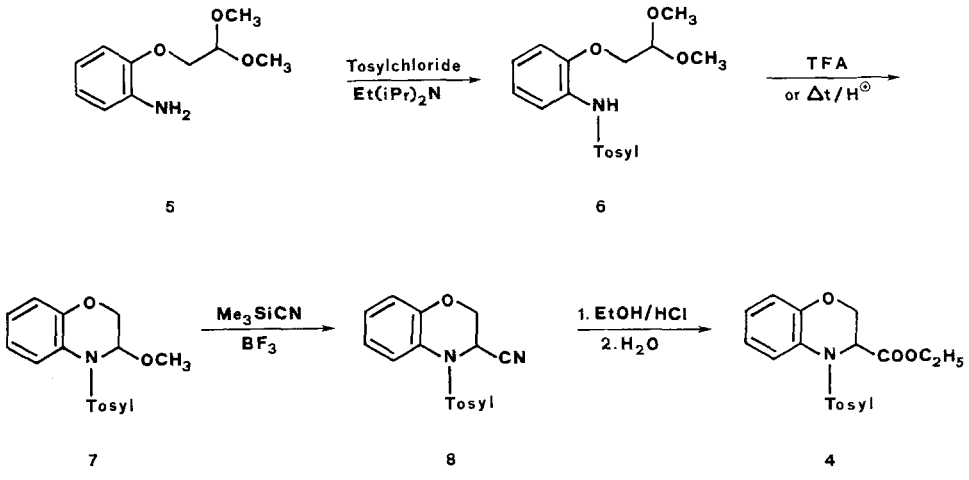


Table 1 compares the chemical shifts of **3** with those of **4**. Whereas the data of the corresponding carboxylic acid, obtained from the ester [3] are in agreement with those of **3**, the paramagnetic shift of the X-part in the ^{1}H-NMR spectrum of **4** represents a remarkable difference.

Table 1. *Chemical shifts (δ) of the ABX-systems of the isomeric esters* **3** *and* **4**

Compound	A-part	B-part	X-part
3	H-3 3.99	H-3 3.47	H-2 4.48
4	H-2 4.57	H-2 3.52	H-3 5.11

Based on these experimental details it could be shown also by chemical methods, that the structure of the reaction product from **1** and **2** was erroneous [3].

Experimental

Melting points were determined on a *Kofler* hot plate apparatus and are uncorrected. Mass spectra were recorded on a Varian MAT-311 instrument and ^{1}H-NMR spectra on a Varian EM 390 (90 MHz) spectrometer (*TMS*, δ/ppm).

2-(2-Tosylaminophenoxy)-1,1-dimethoxyethane (**6**)

A mixture of 1.97 g (10 mmol) **5** [4], 1.55 g (12 mmol) ethyldiisopropylamine and 1.90 g (10 mmol) *p*-toluenesulfonyl chloride in 50 ml toluene was heated for 20 h at 70 °C. The solution was washed with a 5% aqueous solution of sodium hydrogen carbonate and water, dried, evaporated to dryness and the residue was crystallized from methanol to yield 3.35 g (90%) **6**, m.p. 92 °C.

^{1}H-NMR ($CDCl_3$): 2.27 (s, 3 H, CH_3), 3.36 (s, 6 H, 2 OCH_3), 3.71 (d, J = 5 Hz, 2 H, OCH_2), 4.44 (t, J = 5 Hz, 1 H, CH), 7.31 (br. s, 1 H, NH), 6.60–7.60 (m, 8 H, aromatic H).

MS (*m*/e): 351 (M^+, 6%), 319 (4), 164 (18), 75 (100).

$C_{17}H_{21}NO_5S$ (351.4). Calcd. C 58.10 H 6.02 N 3.99.
Found. C 58.01 H 5.85 N 4.18.

3,4-Dihydro-3-methoxy-4-tosyl-2H-1,4-benzoxazine (**7**)

a) To a solution of 3.51 g (10 mmol) **6** in 100 ml dichloromethane 10 ml trifluoroacetic acid was added at 0 °C. After stirring for 2.5 h at 0 °C, the mixture was poured into an ice-cold, saturated solution of sodium hydrogen carbonate. The organic layer was separated, dried and evaporated. Recrystallization from 75% methanol yielded 2.49 g (78%) **7**, m.p. 95–96 °C.

^{1}H-NMR ($CDCl_3$): 2.29 (s, 3 H, CH_3), 3.28 and 4.21 (AB-part of an ABX-system, 2 H, J_{AX} = 1.5 Hz, J_{BX} = 2 Hz, J_{AB} = 12 Hz, OCH_2), 3.41 (s, 3 H, OCH_3), 5.31 (X-part, 1 H, NCH), 6.83–7.83 (m, 8 H, aromatic H).

MS (*m*/e): 319 (M^+, 36%), 164 (100).

$C_{16}H_{17}NO_4S$ (319.4). Calcd. C 60.17 H 5.37 N 4.39.
Found. C 60.30 H 5.39 N 4.38.

b) The solution of 3.51 g (10 mmol) **6** and 86 mg (0.5 mmol) *p*-toluenesulphonic acid in 150 ml toluene was heated at 75 °C. The reaction was monitored by thinlayer chromatography (toluene/ethyl acetate, 6 : 4). After completion of the reaction, the solution was washed with a saturated solution of sodium hydrogen carbonate and water, dried and evaporated. Recrystallization from 75% methanol yielded 3.03 g (95%) **7**, m.p. 96 °C.

3,4-Dihydro-4-tosyl-2H-1,4-benzoxazine-3-carbonitrile (**8**)

To a solution of 3.19 g (10 mmol) **7** and 0.2 ml borotrifluoride etherate in 80 ml ether, 0.99 g (10 mmol) trimethylsilylcyanide was added dropwise at 20 °C. After stirring for 24 h the addition of borotrifluoride etherate and trimethylsilylcyanide (equal amounts as above) was repeated. After completion of the reaction

(thinlayer chromatographic control: cyclohexane/ethyl acetate, 7:3) the mixture was washed with a saturated solution of sodium hydrogen carbonate and water, dried and evaporated. Recrystallization from methanol yielded 2.89 g (92%) **8**, m.p. 87–88 °C.

^{1}H-NMR ($CDCl_3$): 2.46 (s, 3 H, CH_3), 3.70 and 4.44 (AB-part of an ABX-system, 2 H, $J_{AX} = 2$ Hz, $J_{BX} = 3$ Hz, $J_{AB} = 12$ Hz, OCH_2), 5.58 (X-part, 1 H, NCH), 6.58–7.85 (m, 8 H, aromatic H).

MS (*m*/e): 314 (M^+, 17%), 159 (100).

$C_{16}H_{14}N_2O_3S$ (314.4). Calcd. C 61.13 H 4.49 N 8.91.
Found. C 61.04 H 4.67 N 8.70.

Ethyl 3,4-dihydro-4-tosyl-2H-1,4-benzoxazine-3-carboxylate (**4**)

To a solution of 3.14 g (10 mmol) **8** in 150 ml ethanol 0.54 g (15 mmol) hydrogen chloride was introduced at 20 °C. After heating for 24 h at 60 °C the mixture was poured into water and extracted with ether. The etheral solution was washed with a saturated solution of sodium hydrogen carbonate and water, dried and evaporated. From 70% ethanol 3.43 g (95%) **8** were obtained, m.p. 95–96 °C.

^{1}H-NMR ($CDCl_3$): 1.14 (t, 3 H, $J = 7$ Hz, CH_3), 2.34 (s, 3 H, CH_3), 3.52 and 4.57 (AB-part of an ABX-system, 2 H, $J_{AX} = 2$ Hz, $J_{BX} = 3.5$ Hz, $J_{AB} = 12$ Hz, OCH_2), 4.12 (qu, 2 H, $J = 7$ Hz, OCH_2), 5.11 (X-part, 1 H, NCH), 6.79–7.00 (m, 3 H, aromatic H), 7.23 and 7.59 (AB-system, 4 H, $J_{AB} = 7.5$ Hz, tosyl-H), 7.65–7.85 (m, 1 H, aromatic H).

MS (*m*/e): 361 (M^+, 33%), 288 (11), 206 (29), 134 (100).

$C_{18}H_{19}NO_5S$ (361.4). Calcd. C 59.82 H 5.30 N 3.88.
Found. C 59.94 H 5.28 N 3.97.

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