Unusual Tosyl Transfer Solvolysis Reaction to 3-*n*-Butyl-4-methyl-5,5-di-*p*-toluenesulfonyl-3-pyrrolin-2-one

Zachary R. Woydziak, Brian J. Frost and David A. Lightner*

Department of Chemistry, University of Nevada
Reno, NV 89557-0020

Received November 23, 2004

The title compound (**1**) was isolated in 20-30% recovery following solvolysis of a mixture of 5-bromo-3-*n*-butyl-4-methyl-2-*p*-toluenesulfonylpyrrole (**4b**) and 5-bromo-4-*n*-butyl-3-methyl-2-*p*-toluenesulfonylpyrrole (**4a**) in trifluoroacetic acid and water, a reaction designed to produce 5-*p*-toluenesulfonyl-3-pyrrolin-2-ones, *e.g.*, **5a** and **5b**.

J. Heterocyclic Chem., **42**, 731 (2005).

In the 1990s the Barton-Zard pyrrole-forming reaction [1] between nitro-olefins and isocyanides presented a significant advance in pyrrole synthesis, and the reaction was used extensively by Inomata *et al*. [2,3] and others in their syntheses of linear tetrapyrroles [4]. In such work, an interesting and synthetically-useful regio-isomerism was demonstrated: *intra*-molecular migration of a *p*-toluenesulfonyl (tosyl) groups occurred under acid (trifluoroacetic acid) catalysis [2,5]. This turned out to be a convenient route to otherwise difficultly-prepared pyrroles, *e.g.*, 3-methyl-4-phenyl-2-*p*-toluenesulfonylpyrrole (**2b**) from its more readily synthesized (Barton-Zard) regio-isomer **2a** [6], see Figure 1. The distribution of regio-isomers favors that with the tosyl group adjacent to the smaller pyrrole β-substituent; in this case, methyl. Thus, the ratio of **2a**:**2b** is ~5:95 at equilibrium when methyl and phenyl [6] (or *p*-tolyl [5]) are the pyrrole β-substituents, and the dominant isomer is purified easily by crystallization. When both β-substituents are alkyl, as in methyl and *n*-butyl (Figure 1), in our studies of *exo* and *endo*-*n*-butylmesobilirubins [7] we found that the ratio of **3a**:**3b** was ~20:80, and the mixture did not separate well. In that work, we made pure **3a** and pure **3b** separately from valeraldehyde and 1-nitropropane (to **3a**) and acetaldehyde and nitroethane (to **3b**) using Barton-Zard reactions.

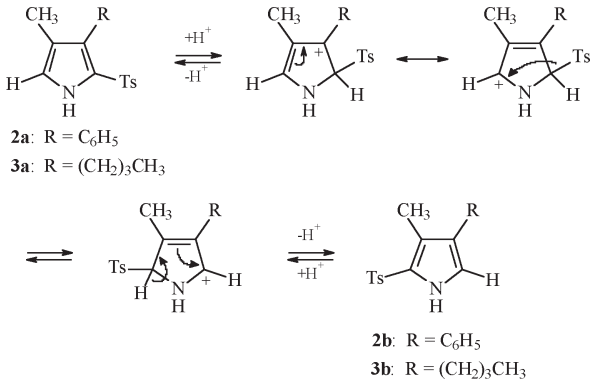


Figure 1. Acid-catalyzed isomerization (reference 2) of regio-isomeric α-*p*-toluenesulfonylpyrroles **2a** and **2b**, and **3a** and **3b** (Ts = *p*-toluenesulfonyl; **2**: R = C_6H_5; **3**: R = $(CH_2)_3CH_3$).

Our interest in tosylpyrroles such as **2** and **3** was as relay compounds to the corresponding tosylpyrrolinones, *e.g.*, **5a** and **5b** from **3a** and **3b** (Figure 2). Such tosylpyrrolinones were used in dipyrrinone and tetrapyrrole syntheses [6]. Conversion of **3a** to **5a** and **3b** to **5b** worked well in two steps: bromination at the unsubstituted α-pyrrole position to afford **4**, which gave **5** following treatment with trifluoracetic acid then water [7]. Although **4a** and **4b** were prepared separately [6], we recently discovered that they could be separated by crystallization, whereas their tosylpyrrol precursors **3a** and **3b** could not. In order to determine whether the tosylpyrrolinone mixture **5a**+**5b** might also be separated by crystallization or chromatography, we isomerized **3a** to give a mixture of **3a**+**3b** and then brominated the mixture to give a mixture of **4a**+**4b**, which was partially purified of extraneous by-products using chromatography. Treatment of the **4a**+**4b** mixture with trifluoroacetic acid and quenching with water afforded a nicely crystalline product, albeit in only 20-30% crude recovery. Purification by recrystallization gave, unexpectedly, the unusual di-tosylpyrrolinone **1**. Apparently **1** was formed by *inter*-molecular transfer of a tosyl group, as in Figure 3, from protonated **4a**-$\mathbf{H}^+$ to **4b**. The regio-isomeric di-tosyl-

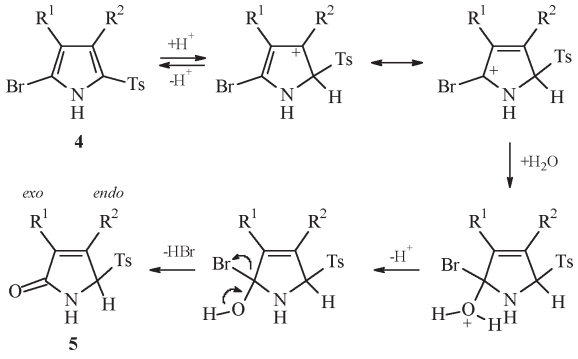


Figure 2. Acid-catalyzed conversion of α-bromo-α'-*p*-toluenesulfonylpyrroles (**4**) to 5-*p*-toluenesulfonyl-3-pyrrolin-2-ones (**5**). For series **a**: $R^1 = CH_3$, $R^2 = (CH_2)_3CH_3$ and for **b**: $R^1 = (CH_2)_3CH_3$, $R^2 = CH_3$.

pyrrolinone was not observed, suggesting that the more sterically-crowded tosyl group (as in **4a**) migrates to the less sterically-crowded bromopyrrole (as in **4b**) to leave behind **6a** and produce **7b**. The latter proceeds during the solvolysis to yield product **1**. Thus, tosyl transfer occurs selectively, **4a-H**$^+$ and **4b** → **6a** and **7b**, but the alternative reaction **4a** and **4b-H**$^+$ → **7a** and **6b** does not.

The structure of ditosylpyrrole **1** was confirmed by nmr spectroscopy and X-ray crystallography. The C-13 nmr singlet resonance at 170.8 ppm confirmed a successful conversion of **4b** to a pyrrolinone, the singlet resonances at 141.5 and 146.7 ppm confirmed the presence of the 3-pyrrolin-2-one carbon-carbon double bond, and the singlet resonance at 95.6 confirmed the fourth ring carbon to which the two tosyl groups are attached (Table 1). One may compare C-13 nmr data from the corresponding regio-isomeric mono-tosylpyrrolinones **5a** and **5b** (Table 1). Thus, **5b** shows

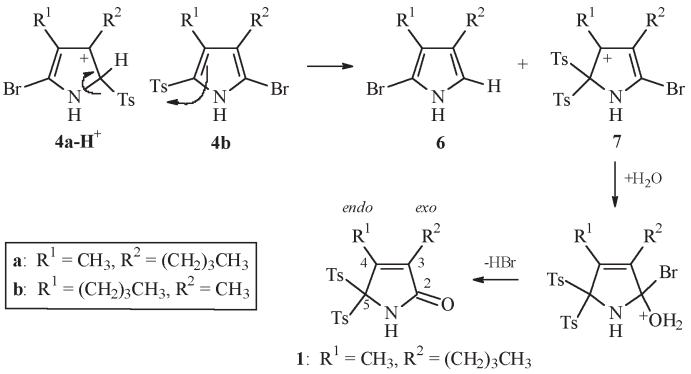
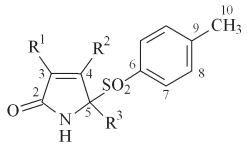


Figure 3. Tosyl transfer from protonated **4a** (Figure 2) to bromotosylpyrrole **4b** to form bromopyrrole **6** and di-tosyl intermediate **7**. The last reacts with water to give **1**.

Table 1

Comparison of the C-13 and H-nmrchemical shifts [a] and assignments of tosylpyrrolinones.



Carbon		C-13			H-1		
		1 [b]	**5a** [c]	**5b** [d]	**1** [b]	**5a** [c]	**5b** [d]
2	C=O	170.8	173.7	173.1	–	–	–
3	=C–	141.5	133.9	138.6	–	–	–
3^1	CH_2 or CH_3	29.4	8.6	30.1	1.88 t (7.1)	1.57 s	1.92 m
3^2	CH_2	23.3	–	23.3	0.92 m	–	0.97 m
3^3	CH_2	22.2	–	22.5	0.76 m	–	0.91 m
3^4	CH_3	12.3	–	14.0	0.73 t (7.5)	–	0.75 t (6.3)
4	=C–	146.7	147.9	146.1	–	–	–
4^1	CH_3 or CH_2	13.7	30.8	13.1	2.35 s	2.72 m	2.14 s
4^2	CH_2	–	22.7	–	–	1.38 m	–
4^3	CH_2	–	26.9	–	–	1.38 m	–
4^4	CH_3	–	13.8	–	–	0.95 t (8.3)	–
5	C	95.6	77.5	79.3	–	5.11 s	5.02 s
6	–C=	132.2	131.1	130.9	–	–	–
7	–C=	130.1	129.8	129.9	7.32 d (8.1)	7.30 d (7.8)	7.30 d (8.3)
8	–C=	129.6	129.6	129.7	7.66 d (8.1)	7.64 d (7.8)	7.67 d (8.3)
9	–C=	142.3	145.9	143.1	–	–	–
10	CH_3	21.7	21.8	21.8	2.25 s	2.42 s	2.41 s
	NH	–	–	–	6.51 s	6.28 s	6.53 s

[a] In ppm downfield from tetramethylsilane for 1 x 10^{-2} *M* solutions at 22 °C in deuteriochloroform: numbers in parentheses are coupling constants (J, Hz); [b] $R^1 = (CH_2)CH_3$, $R^2 = CH_3$, R^3 = tosyl; [c] $R^1 = CH_3$, $R^2 = (CH_2)_3CH_3$, R^3 = H, from reference 7; [d] $R^1 = (CH_2)_3CH_3$, $R^2 = CH_3$, R^3 = H, from reference 7.

173.1 (s, C=O), 146.1 (s, C-4), 143.1 (s, C-3) and 79.3 (d, C-5) ppm; whereas, **5a** shows 173.7 (s, C=O), 147.9 (s, C-4), 133.9 (s, C-3) and 77.5 (d, C-5) ppm. The isomeric mono-tosylpyrrolinones show distinctly different pyrrolinone ring methyl groups in their nmr spectra. In the C-13 nmr, the *exo*-methyl of **5a** appears at 8.6 ppm, and the *endo*-methyl of **5b** at 13.1 ppm. In **1** it lies at 13.7 ppm. In the H-nmr, the *exo*-methyl of **5a** appears at 1.57 ppm, and the *endo*-methyl of **5b** at 2.14 ppm. The correspondiing methyl resonance in **1** is found at 2.35 ppm. The C-13 and H-nmr data for the ring methyl resonances of **1** correlate better with the *endo*-methyl of **5b**.

Final proof of the structure of **1** comes from its X-ray crystallographic structure (Figure 4). X-ray quality crystals of **1** were grown by slow evaporative diffusion of hexane into chloroform [8]. In the crystal, both *p*-toluenesulfonyl groups are oriented *syn* to the pyrrolinone such that the plane of the pyrrolinone unit is sandwiched between the *p*-tolyl planes, leaving the sulfones essentially eclipsed. The *n*-butyl group at C(3) has an extended conformation. The internal angles of the planar pyrrolinone, N(1)-C(1)-C(2) = 105.6°, C(1)-C(2)-C(3) = 109.0°, C(2)-C(3)-C(4) = 110.3°, C(3)-C(4)-N(1) = 101.6° and C(1)-N(1)-C(4) = 113.4°, are not unusual and are close to those predicted by molecular mechanics (PCMODEL) [9]: 105.9°, 107.9°, 112.1°, 99.5°, 114.5°, respectively. Other bond angles, and bond lengths appear to be normal for toluenesulfonyl and pyrrolinone systems.

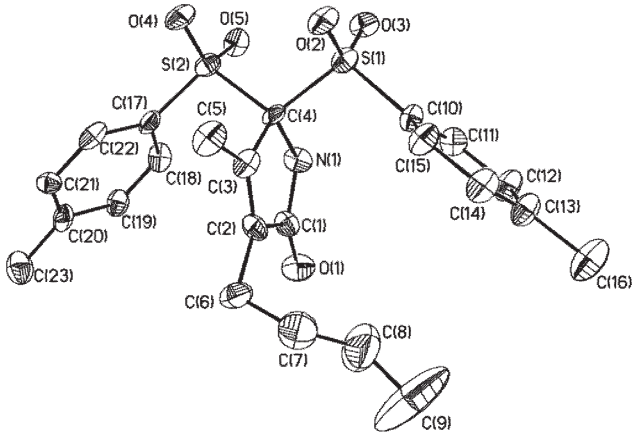


Figure 4. Thermal ellipsoid representation of **1** including the atomic numbering scheme. Hydrogen atoms have been omitted for clarity. Thermal ellipsoids are drawn at 50% probability.

EXPERIMENTAL

Nuclear magnetic resonance (nmr) spectra were obtained on a GE QE-300 spectrometer operating at 300 MHz (proton) and 75 MHz (C-13), respectively, in deuteriochloroform. Chemical shifts are reported in ppm referenced to the residual chloroform proton signal at 7.26 ppm and C-13 signal at 77.23 ppm unless otherwise noted. Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected. Analytical thin layer chromatrography (tlc) was carried out on J.T. Baker silica gel IB-F plates (125 μm layer). For purification, radial chromatography was carried out on Merck silica gel PF_{254} with calcium sulfate binder, preparative layer grade. All solvents were reagent grade obtained from Fisher or Aldrich; deuterated chloroform was from Cambridge Isotope Laboratories. 3-*n*-Butyl-4-methyl-2-*p*-toluenesulfonyl-1*H*-pyrrole (**3a**) was synthesized according to the literature procedure [7]. Crystal structure atomic coordinates of **1**, tables of bond lengths, bond angles and torsion angles are available from the Cambridge Structural Data File (CCDC No. 255164) [8].

4-*n*-Butyl-3-methyl-5,5-di-*p*-toluenesulfonyl-3-pyrrolin-2-one (**1**).

3-*n*-Butyl-4-methyl-2-tosylpyrrole **3b** [7] (7.0 g, 0.0241 mol) was dissolved in 200 ml of 10% trifluoroacetic acid-90% dichloromethane (vol:vol) and stirred for a period of 24 hours to give an 80:20 mixture of **3a**+**3b**. To the resulting dark blue solution was added 100 ml of dichloromethane, and the solution was washed sequentially with 2 x 100 ml of water, 1 x 100 ml of saturated aqueous sodium carbonate solution (using a small amount of brine solution to break up emulsions), and 1 x 100 ml of brine solution. The organic solution was then dried over anhydrous sodium sulfate and removed (rotovap) to give a crude blue oil. The oil was decolorized by filtering through a short column of silica, eluting with dichloromethane. The recovered pale yellow oil was stored at -20 °C for 12 hours; then, it was dissolved in 50 ml of dichloromethane and cooled to -5 °C using an ice-salt bath. This solution was titrated with 1.06 g (0.02 mol) of bromine in 30 ml of dichloromethane over the course of 20 minutes. The resulting solution of **4a**+**4b** was allowed to stir for 20 minutes (at -5 °C) before being quenched with 10% aqueous ammonia, which was added dropwise over 20 minutes. The aqueous layer was separated from the organic layer and extracted three times with 50 ml portions of dichloromethane. The combined organic fractions were washed with 2 x 100 ml of saturated aqueous sodium carbonate, 100 ml of water and 100 ml of brine solution then dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated (rotovap). The crude brown oily product (**4a**+**4b**) was taken up in 70 ml of trifluoroacetic acid, then 11.6 ml of water was added dropwise to the stirred solution over about 20 minutes. When all the water had been added, the solution was allowed to stir for an additional 4 hours before being taken up into 200 ml of dichloromethane. The solution was washed sequentially with water (2 x 200 ml), saturated aqueous sodium carbonate (2 x 200 ml) and brine (100 ml) before being dried over anhydrous sodium sulfate, filtered and evaporated (rotovap). The resulting brown oil was crystallized from dichloromethane-*n*-hexane to give a solid, which was further purified by radial chromatography on silica gel (1:1 hexane-ethyl acetate eluent, or 2% methanol in dichloromethane) to give 1.0 g (0.002 mol) of **1**, in an overall 18% yield for the three-step reaction from **3a**. It had m.p. 203-206 °C; C-13 and H-nmr shown in Table 1 and an X-ray crystallographic structure shown in Figure 4.

Anal. Calcd for $C_{23}H_{27}NO_5S_2$ (461.6): C, 59.84; H, 5.90; N, 3.03. Found: C, 59.74; H, 5.70; N, 3.10.

REFERRENCES AND NOTES

[1] D. H. R. Barton, J. Kervagoret and S. Z. Zard, *Tetrahedron*, **46**, 7587 (1990).

[2] H. Kinoshita, Y. Hayashi, Y. Murata and K. Inomata, *Chem. Lett*., 1437 (1993).

[3] S. Takeda, K. P. Jayasundera, T. Kakiuchi, H. Kinoshita and K. Inomata, *Chem. Lett*., 590 (2001).

[4] H. Falk, The Chemistry of Linear Oligopyrroles and Bile Pigments, Springer-Verlag, Vienna, 1989, and references therein.

[5] K. Kohori, H. Kinoshita and K. Inomata, *Chem. Lett*., 799 (1995).

[6] J. O. Brower, D. A. Lightner and A. F. McDonagh, *Tetrahedron*, **57**, 7813 (2001).

[7] J. O. Brower, D. A. Lightner and A. F. McDonagh, *Tetrahedron*, **56**, 7869 (2000).

[8] CCDC 255164 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] PCModel vers. 8.5, Serena Software, Bloomington, IN, USA.