

Tosylation of 2-(Monosubstituted)amino-1,3,4-thiadiazoles

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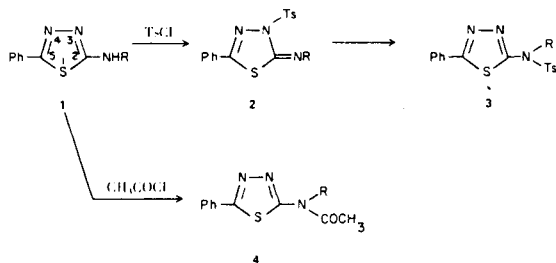
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Tosylation of 2-benzylamino- and 2-anilino-5-phenyl-1,3,4-thiadiazoles (**1a,b**) in the presence of triethylamine affords the ring-sulfonylated products **2a,b** which isomerize in a later stage of the reaction to the exocyclic amino-sulfonylated products **3a,b**. Acetylation of **1a,b** gives the acylamino substituted thiadiazoles **4a,b** directly as the only reaction products. The ^{13}C nmr data are discussed and their importance for the study of prototropic tautomerism and for structure elucidation of the reaction products is indicated.

J. Heterocyclic Chem., **14**, 515 (1977).

2-(Monosubstituted)amino-1,3,4-thiadiazoles (**1**) are ambident nucleophiles (**1**) which have been alkylated and acylated on the endocyclic and/or exocyclic nitrogen atoms (**2**). We have found that tosylation of **1a** in the presence of triethylamine afforded **2a** (m.p. 155-158°) which slowly isomerized into **3a** (m.p. 197-198°) upon standing in chloroform. Compound **1a** was regenerated from **2a** but not from **3a** by methanolysis. In contrast to tosylation, acetylation of **1a** with acetyl chloride in the presence of triethylamine furnished **4a** (m.p. 122-124°) directly.



a: R = PhCH₂; b: R = Ph

The structure of all the products was firmly established by ^1H and ^{13}C nmr spectra as outlined below (see also Table 1). The exact tautomeric structure of **1a** in DMSO- d_6 is easily deduced from ^1H nmr spectroscopy. Indeed, the spectrum showed a triplet at δ 8.6 ppm for the NH proton, coupled with the benzyl protons which resonate as a doublet at δ 4.6 ppm ($^3J_{\text{HCNH}} = 5$ Hz). The ring carbon absorptions of **1a** in the ^{13}C nmr spectrum are found at δ 168.8 (C_2) and 156.6 ppm (C_5).

An inspection of the ring carbon absorptions listed in discloses that **3a** and **4a** must have ring skeleton different from **2a**. Measurements of the coupling constant $^1J_{\text{C-H}}$ for the benzyl methylene group substantiates the struc-

Table 1

 ^{13}C Nmr Data (δ Values in ppm from TMS) (a)

Compound	C_2	C_5	Other shift values
1a	168.8	156.6	CH_2 at 48 ($^1J_{\text{C-H}} = 139$ Hz)
1b	164.5 (b)	157.9 (b)	Ph-N C_1 at 140.9, C_o at 117.8, C_p at 122.3
2a	151.5 (b)	149.5 (b)	CH_3 at 21.6, CH_2 at 62.3 ($^1J_{\text{C-H}} = 135$ Hz)
2b	152.1 (c)	149.7 (c)	CH_3 at 21.8, Ph-N C_1 at 151.2, C_o at 120.6, C_p at 125.3
3a	161.7	166.5	CH_3 at 21.6, CH_2 at 53.3 ($^1J_{\text{C-H}} = 142$ Hz)
3b	163.6 (d)	166.7 (d)	Ph-N C_1 at 138.5, $\text{C}_{o,m,p}$ at 127-130, CH_3 at 21.7
4a	160.1 (d)	165.4 (d)	CH_3 at 22.4, CH_2 at 51.6 ($^1J_{\text{C-H}} = 141.5$ Hz) $\text{C}=\text{O}$ at 170.5
4b	160.8 (d)	164.6 (d)	CH_3 at 23.2, $\text{C}=\text{O}$ at 169.9, Ph-N C_1 at 139.5, $\text{C}_{o,m,p}$ at 127-130

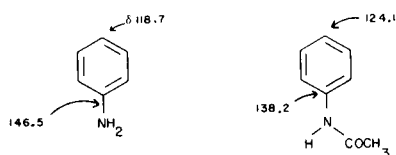
(a) All the spectra were recorded in deuteriochloroform except those of compounds **1a,b** which were taken in DMSO- d_6 . (b) Assignment by selective decoupling. (c) Absorptions are tentatively assigned. (d) Assignment by an examination of the undecoupled spectrum.

tures. Indeed, $^1J_{\text{C-H}}$ is known to be related to the extent of charge localization on the nitrogen atom (**3**). In **3a** and **4a** the amino methylene group exhibits a coupling constant of ca 142 Hz, whereas the methylene group in

2a has $^1J_{C-H} = 135$ Hz. This is in line with the downfield chemical shift of the methylene protons in the 1H nmr spectra of **3a** (δ 5.17) and **4a** (δ 5.57) compared with **2a** (δ 4.40), which is to be expected since the electron density on the exocyclic nitrogen atom in the first two cases is strongly decreased by amidine-type resonance. The shift values of the CH_2 carbon absorptions in the ^{13}C nmr spectra (see Table I) also point to this conclusion. Additional evidence for **4a** is provided by the uncoupled ^{13}C nmr spectrum which shows a complex pattern (q x t) for the $C=O$ carbon absorption (δ 170.5 ppm) due to coupling over two and three bonds ($PhCH_2N-COCH_3$).

The ^{13}C nmr data given above can now be used as a powerful tool for elucidating the tautomeric structure (4) of the ambident starting materials as well as the structure of the reaction products. For instance, **1b** exhibits similar ring-carbon resonances in DMSO- d_6 as **1a** (see Table I), indicating that the same tautomeric form is present. Similarly, **2b**, **3b** (m.p. 155°) and **4b** (5), prepared by tosylation and acetylation of **1b**, can be identified on the basis of the ring-carbon absorptions (see Table I). For **2b** the phenylimino structure is further substantiated by the expected low field absorption of the aromatic C_1 atom (δ 151.2 ppm) and the high field absorptions of the C_o (δ 120.6 ppm) and C_p atoms (δ 125.3 ppm). In **3b** and **4b** all the CH aromatic carbons absorb at δ 127-130 ppm.

If we compare the ring carbon absorptions of **3a,b** and **4a,b** with those of **1a,b** in Table I, we notice an upfield shift at C_2 and a downfield shift at C_5 by replacing H for an electron-withdrawing substituent. This parallels the observed shifts for C_1 and C_p when aniline is acetylated as shown below:



EXPERIMENTAL

Procedure for the Synthesis of **2a** and **3a**.

A benzene solution (80 ml.) of **1a** (m.p. $183-185^\circ$) (5) (0.01 mole), tosyl chloride (0.01 mole) and triethylamine (1 g.) was refluxed for 12 hours. After removal of the salt, the filtrate was evaporated and the residue was crystallized from ether (40 ml.) to give **2a** in ca 90% yield, m.p. $155-158^\circ$ (chloroform-ether); ir (potassium bromide): 1645 cm^{-1} .

Anal. Calcd. for $C_{22}H_{19}N_3O_2S_2$ (421): C, 62.71; H, 4.51; N, 9.98. Found: C, 62.62; H, 4.51; N, 10.09.

When **2a** (4.21 g.) was allowed to stand in chloroform (50 ml.) for two months, **3a** crystallized out in 68% yield, m.p. $197-198^\circ$ (chloroform). The reaction residue was shown to contain unchanged **2a** together with its hydrolyzed product.

Anal. of **3a** Calcd. for M^+ (determined by high-resolution exact-mass measurements): 421.09185. Found: 421.09177.

Similar treatment of **1b** (m.p. 141°) (5) with tosyl chloride and triethylamine at 75° yielded **2b** in very small amounts (10%, m.p. $134-135^\circ$), but when the reaction was carried out in toluene (50 ml.) without base at reflux temperature for 6 days, **3b** was obtained after column chromatography on alumina with benzene as the eluent, yield 40%, m.p. $155-156^\circ$ (ether-chloroform).

Anal. Calcd. for M^+ : 407.0760. Found: 407.0783.

Synthesis of **4a**.

A benzene solution (80 ml.) of **1a** (0.01 mole), acetyl chloride (0.02 mole) and triethylamine (1 g.) was heated for 20 hours at 50° . After removal of the salt, the filtrate was evaporated and the residue was crystallized from ether to give **4a** in 55% yield, m.p. $122-124^\circ$ (ether-chloroform); ir (potassium bromide): 1675 cm^{-1} .

Anal. Calcd. for M^+ : 309.0934. Found: 309.0914.

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REFERENCES AND NOTES

- (1) For a recent discussion of the properties of ambident nucleophiles, see R. Grompper and H. U. Wagner, *Angew. Chem.*, **88**, 389 (1976); *Angew. Chem., Int. Ed. Engl.*, **15**, 321 (1976).
- (2) J. Sandström, *Adv. Heterocyclic Chem.*, **9**, 181-182 (1968); G. Werber, F. Buccheri, and N. Vivona, *J. Heterocyclic Chem.*, **12**, 841 (1975).
- (3) P. Haake, W. B. Miller, and D. A. Tyssee, *J. Am. Chem. Soc.*, **86**, 3577 (1964).
- (4) For a discussion of the methods used so far to elucidate tautomeric structures, see A. R. Katritzky and J. M. Lagowski, *Adv. Heterocyclic Chem.*, **1**, 311 (1963).
- (5) This compound was prepared by the method of W. Marchwald and A. Bott, *Ber.*, **29**, 2914 (1896).