Tosylation of *N,N,N''*-Trisubstituted Formamidrazones: *N'*-Tosylformamidrazones and *N*-Tosylformohydrazide

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In connection with our interest in sulfonylformamidrazones [1,2] we have investigated the formation and stability of the hitherto unknown *N'*-sulfonylformamidrazones.

Results. *N'*-Tosylated formamidrazones *2* were obtained from equimolar amounts of *N,N,N''*-trisubstituted formamidrazones *1* and *p*-toluenesulfonyl chloride with excess triethylamine in ethanol, benzene or toluene solution (Scheme 1). The yields of *2* varied from 49 to 95 %.

The structure of the compounds *2* was confirmed by the spectral data and determination of the hydrolysis products (see below). The ^{13}C NMR and ^{1}H NMR spectra of *2b* and *2c* showed only one set of signals in DMSO indicating only one isomer in solution, in contrast to the findings for *N''*-tosylated formamidrazones [1,2] where two rotamers were found. Compound *2a* gave also one set of ^{13}C NMR signals in DMSO while the ^{1}H NMR spectrum showed a doubling of the $CH_3N=C$ and the $N=CH$ proton signals, indicating hindered rotation or the presence of *Z/E* isomers.

Compound *2d* could not be obtained in completely pure state; it decomposed on standing and was normally contaminated with *N'N'*-dimethyl-*p*-toluenesulfonohydrazide, and it was not possible to determine the number of isomers in solution. Attempts to purify *2d* by distillation, recrystallization or TLC separation resulted in decomposition. *2d* is obviously the main product as seen from the hydrolysis results, giving more than 70 % of the sulfonohydrazide *5d*. The IR and MS data are in accordance with the proposed structure.

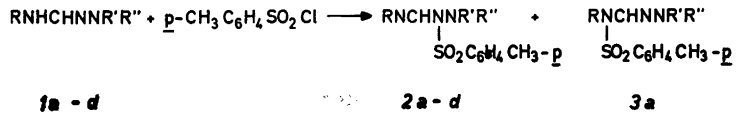
The *N'*-tosylated formamidrazones turned out to be unstable on silica gel plates. Attempts to isolate possible *N''*-tosylated compounds by TLC separations of the filtered and evaporated reaction mixture resulted in decomposition to give *N*-tosylated formohydrazide *4* and *N'N'*-disubstituted *p*-toluenesulfonohydrazide *5*. Only for *1a* could a small amount of *N'*-tosylated compound *3a* [1] be isolated.

Hydrolysis of *2a–d* in 1 M HCl at room temperature also gave compounds *4* and/or *5* (Scheme 2). The identity of the products was established by IR and NMR spectra identical with those of authentic specimen.

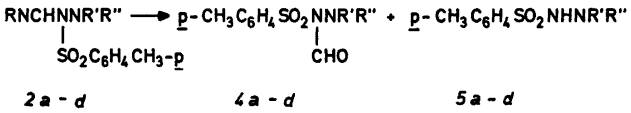
N-Tosyl-*N',N'*-dimethyl formohydrazide *4b* was prepared unambiguously by formylation of *N,N*-dimethyl-*p*-toluenesulfonohydrazide with acetic formic anhydride (Scheme 3).

Experimental. The instrumental equipment was reported earlier.[1]

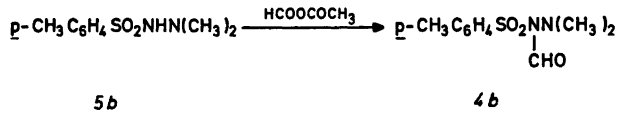
Tosylation of N,N''-*dimethyl*-N-*phenylformamidrazone* 1a. *p*-Toluenesulfonyl chloride (0.033 mol), triethylamine (0.066 mol) and *1a* [3] (0.033 mol) were mixed in benzene (70 ml) and stirred at room temperature overnight.



Scheme 1. R = Me (*a*), Ph (*b,c*), C_6H_{11} (*d*); R' = Me (*a–d*); R'' = Ph (*a,c*), Me (*b,d*).



Scheme 2.



Scheme 3.

The precipitate of triethylammonium chloride was filtered off and the filtrate evaporated, giving 4.3 g of a red-orange oil. This oil was dissolved in H_2O, extracted with CH_2Cl_2, dried over K_2CO_3 and evaporated. Yield 60 % of *N³-methyl-N²-phenyl-N¹-tosylformohydrazide methylimide 2a*, m.p. 104–105 °C (from ethanol), Anal. $C_{16}H_{19}N_3O_2S$: C, H, N, S. MS *m/e* (% of base peak): 317(7) (M^+), 213(7), 163(13), 162(100), 122(7), 121(77), 106(23), 92(11), 91(13), 77(46), 65(9), 42(26). ^{13}C NMR (DMSO-d_6): δ 148.0 (C(1) in *N³*-Ph group); 145.1 (CH=N); 144.8 (C(1) in SO_2-Ph group); 134.7 (C(4) in Tos-group); 130.2, 128.4, 127.9, 119.3, 112.7 (tertiary C atoms in the benzene rings); 42.0 ($CH_3N=$); 38.8 (NCH_3); 21.0 (*p*-CH_3). ^1H NMR ($CDCl_3$): δ 8.14 and 8.12 (1 H, singlets, intensity *ca.* 2/1); 7.8–6.4 (9 H, m); 3.09 and 3.06 (3H, singlets, intensity *ca.* 2/1); 2.93 (3 H, s); 2.36 (3 H, s). IR (KBr, cm^{-1}): 2960w, 2965w, 1662s, 1595s, 1580w, 1496s, 1485w, 1370s, 1442m, 1185m, 1170s, 1150m, 1120w, 1100m, 1088m, 951s, 755s, 662s, 580s.

TLC separations on the red-orange oil on silica gel plates with $CHCl_3$/light petroleum (1/1) as eluent gave three components. One was identified as *N¹,N³-dimethyl-N³-phenyl-N¹-(4-methylphenylsulfonyl)formamide hydrazone 3a*.[1] The other identified as *N'-methyl-N'-phenyl-N-tosylformohydrazide* 4a, yield 17 %, identified by means of IR and NMR spectra. The third component was identified as *N'-methyl-N'-phenyl-p-toluenesulfonohydrazide* 5a.[4] Yield 45 %, m.p. 130 °C, Anal. $C_{14}H_{16}N_2O_3S$: C, H, N, S. MS *m/e* (% of base peak): 276(4) (M^+), 122(14), 121(100), 91(10), 77(20). ^1H NMR ($CDCl_3$): δ 7.8–6.7 (10 H, m), 6.43 (1 H, s), 2.90 (3 H, s), 2.40 (3 H, s).

Hydrolysis of 2a. 100 mg of *2a* was dissolved in 1 M HCl (10 ml). After stirring for 0.5 h the precipitate was filtered off. Yield 50 % of *N'-methyl-N'-phenyl-N-tosylformohydrazide* 4a, m.p. 116 °C (from ethanol), Anal. $C_{15}H_{16}N_2O_3S$: C, H, N, S. MS *m/e* (% of base peak): 304(16) (M^+), 150(9), 149(97), 121(44), 106(9), 105(44), 104(22), 93(19), 92(22), 91(36), 78(14), 77(100), 65(31), 51(36), 43(17). ^1H NMR (DMSO-d_6): δ 9.12 (1 H, s broad), 8.0–6.6 (9 H, m), 2.88 (3 H, s), 2.42 (3 H, m).

Tosylation of N,N,-*dimethyl-N''-phenylformamidrazone* 1b. *p*-Toluenesulfonyl chloride (0.046 mol), *1b*[5] (0.046 mol) and triethylamine (0.092 mol) were stirred in abs. ethanol (100 ml) for 5 h. Work-up analogous to *1a* gave 49 % of *N²,N³-dimethyl-N¹-tosylformohydrazide phenylimide* 2b, m.p. 94–95 °C (from ethanol), Anal. $C_{16}H_{19}N_3O_2S$: C, H, N, S. MS *m/e* (% of base peak): 317(1) (M^+), 163(9), 162(64), 106(14), 91(12), 77(21), 65(9), 59(100), 51(68). ^{13}C NMR (DMSO-d_6): δ 149.0 (C(1) in the *N³*-Ph group); 144.8 (C(1) in the SO_2-Ph group); 144.5 (CN=N); 134.0 (C(4) in the Tos-group); 129.9, 129.1, 128.3, 124.8, 121.1 (tertiary C atoms in the benzene rings); 42.6 ($N(CH_3)_2$); 21.1 (*p*-Me). ^1H NMR (DMSO-d_6): δ 8.42 (1 H, s), 7.9–6.9 (9 H, m), 2.77 (6 H, s), 2.45 (3 H, s).

Hydrolysis of 2b. 1 g of *2b* was stirred with 1 M HCl (15 ml) for 3 days at room temperature. After neutralization and extraction with CH_2Cl_2 *N',N'-dimethyl-p-toluenesulfonohydrazide 5b* was isolated, yield 50 %. Identified by IR and ^1H NMR spectra identical with those of an authentic compound.[6] TLC experiments analogous to *2a* resulted in mixtures, probably due to decomposition.

Tosylation of N-*methyl*-N,N''-*diphenylformamidrazone* 1c. *p*-Toluenesulfonyl chloride (0.04 mol), *1c*[5] (0.04 mol) and triethylamine (0.08 mol) were stirred in benzene (70 ml) at room temperature overnight. After filtration of the precipitate the filtrate was evaporated to dryness resulting in 95 % of crude *N³-methyl-N²-phenyl-N¹-tosylformohydrazide phenylimide 2c*, m.p. 88–89 °C, Anal. $C_{21}H_{21}N_3O_2S$: C, H, N. MS *m/e* (% of base peak): 379(6) (M^+), 225(18), 224(68), 122(14), 121(100), 107(14), 106(23), 105(16), 104(11), 93(11), 92(18), 91(20), 78(20), 77(57), 65(16), 51(14). ^{13}C NMR (DMSO-d_6): δ 148.1 and 147.7 (C(1) in *N³*-Ph and *N³*-Ph group); 145.5 (C(1) in SO_2-Ph group); 144.1 (CH=N); 134.2 (C(4) in Tos-group); 130.2, 129.0, 128.5, 128.3, 124.9, 121.2, 119.6, 112.9 (tertiary C atoms in benzene rings); 39.4 (*N³*-Me); 21.1 (*p*-Me). ^1H NMR ($CDCl_3$): δ 8.50 (1 H, s), 7.9–6.6 (14 H, m), 3.12 (3 H, s), 2.42 (3 H, s).

Hydrolysis of 2c. *2c* (0.0026 mol) was stirred in 1 M HCl (15 ml) at room temperature for 2 days. The colourless precipitate was filtered off and recrystallized from ethanol, m.p. 110 °C identified as *4a* by IR and NMR spectra identical with those of an authentic compound. On prolonged hydrolysis at room temperature in excess 1 M HCl a mixture of *4a* and *5a* was formed, identified by ^1H NMR spectrum. TLC of *2c* on silica gel with $CHCl_3$/light petroleum (1/1) as eluent also resulted in mixtures of *4a* and *5a*, which on recrystallization gave *5a* identified by IR and ^1H NMR spectrum.

Tosylation of N''-*cyclohexyl*-N,N-*dimethylformamidrazone* 1d. *p*-Toluenesulfonyl chloride (0.08 mol), *1d* (0.08 mol)[7] and triethylamine (0.16 mol) were stirred in abs. ethanol (100 ml) at room temperature for 1 day. Work-up analogous to *1a* gave a yellow oil (*2d*) impure, yield 80 %. MS *m/e* (% of base peak): 323(5) (M^+), 281(10), 169(20), 168(73), 155(14), 139(10), 125(9), 110(14), 98(39), 91(30), 65(16), 59(100), 55(16). ^1H NMR ($CDCl_3$): δ 8.25 (1 H, s), 8.0–7.1 (4 H, m), 3.6–2.8 (1 H, broad), 2.65 (6 H, s), 2.42 (3 H, s), 2.0–1.0 (10 H, broad). Heating of *2d* in DMSO-solution above 110 °C caused decomposition; below 110 °C no changes were observed in the ^1H NMR signals.

Acid hydrolysis of 2d (1 g) in 1 M HCl (10 ml) for 2 h at room temperature gave cyclohexylamine and *N',N'-dimethyl-p-toluene sulfonohydrazide 5d* (*ca.* 70 %). Attempts to purify *2d* by TLC caused decomposition to *N',N'-*

dimethyl-*N*-tosylformohydrazide (20–30 %) and *N'*,*N'*-dimethyl-*p*-toluenesulfonohydrazide.

N',N'-*Dimethyl*-N-*tosylformohydrazide* 4b. *N'*,*N'*-Dimethyl-*p*-toluenesulfonohydrazide (0.02 mol) was stirred at room temperature for 2.5 h with (0.23 mol) acetic formic anhydride formylating mixture prepared by heating equimolar amounts of acetic acid anhydride and formic acid for 2 h. After cooling to 0 °C the mixture was poured into H_2O (150 ml), the precipitate was filtered off. Yield 80 %, m.p. 79–80 °C (from ethanol), Anal. $C_{10}H_{14}N_2O_3S$: C, H, N. MS *m/e* (% of base peak): 242(9) M+), 91(27), 87(100), 65(25), 59(78), 43(55). ^{1}H NMR ($CDCl_3$): δ 8.96 (1 H, s), 7.8–7.2 (4 H, m), 2.63 (6 H, s), 2.46 (3 H, s).

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An Improved Synthesis of 2-Methyl-4,6-dihydroxybenzoic Acid (Orsellinate) Esters and Homologues

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In connection with ongoing research in this Laboratory directed toward the synthesis of natural products based on the 2-alkyl-4,6-dihydroxybenzoic acid system (*1*), we became attracted by the route[1] shown in Scheme 1 (reagent a). In our hands, however, the reaction failed to give the reported yields. For example, ethyl 2-methyl-4,6-dihydroxybenzoate (orsellinate) *1a* was obtained[1] in 38 % yield whereas our yields were consistently less than 10 %.

Thallium(I) salts of β-dicarbonyl systems have been used for *C*-alkylations and *C*-acylations in very high yields.[2] We were, therefore, led to test the Tl(I) salt of various β-keto esters in the diketene reaction, and now report that ethyl orsellinate and homologues are obtainable in acceptable yields (Scheme 1, reagent b; isolated yields are shown). As seen from the second entry (*1b*), the reaction can be further improved by the use of *t*-butyl[3] instead of ethyl β-keto esters.

Applications of the β-keto ester/Tl(I)/diketene route to the synthesis of naturally occurring orsellinate-type compounds will be reported shortly.

Experimental. General procedure. Thallium(I) salts of β-keto esters were made either with TlOH in aqueous solution[4] or with TlOEt in light petroleum.[5] The crystalline Tl(I) salts were dried for 6 h under high vacuum at 25 °C.

Freshly distilled diketene (0.091 ml, 1.2 mmol) was added with a syringe into 1 mmol of the Tl(I) salt under Ar in THF (CaH_2-dried, 5 ml) at 0 °C. The mixture was stirred for 40 h at 0 °C, poured on 2 N H_2SO_4 (20 ml) and extracted twice with ether. The combined extracts were washed with water, dilute aqueous $NaHCO_3$, dried and evaporated. Preparative TLC (Merck silica gel PF_{254}, elution with $CHCl_3$) then gave the orsellinate or homologue, recrystallized from light petroleum 40–60 °C.

Individual products. The compounds *1a–1d* are known,[1] and had physical properties in accord with their structure and reported data. *Ethyl-2-(8-t-butyldimethylsilyloxynonyl)-4,6-dihydroxybenzoate.* A. Ethyl 7-bromoheptanoate (2.5 g) was treated in dry toluene (50 ml) at −80 °C with diisobutylaluminium hydride (20 % in hexane, 11.0 ml, 1.02 eq). After 5 h at −80 °C, the cold solution was poured with stirring on 2 N H_2SO_4 (50 ml). Extraction (Et_2O) and washing (aqueous $NaHCO_3$), drying and evaporation of the combined organic layers gave crude 7-bromoheptanal (1.85 g), used