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Insights into sulfinate formation from tosyl hydrazides

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ABSTRACT

Benzylation of 1,2-ditosylhydrazine in DMF under various basic conditions results in a benzyl sulfone via intermediary sulfinate formation, providing new insights and allowing practical conclusions to be drawn. The half-lives of 1,2-ditosylhydrazine and several monotosylated hydrazides with 1,1,3,3-tetramethylguanidine in DMSO have been determined by ^{1}H NMR spectroscopy and are found to vary from a few minutes to several months. In the course of this work a benzylated, partly detosylated compound has been identified and a 1,1,3,3-tetramethyl guanidine-containing side-product characterized. A contradictory report is also commented on.

Sulfonyl hydrazides are useful organic reagents of which tosyl hydrazide (tosyl = 4-methylbenzenesulfonyl) is a typical representative that has made possible a multitude of diverse manipulations under mild conditions.[1] Prominent are those taking place via hydrazones and by treatment with bases or reducing agents, leading to alkenes or deoxygenation products and with the reagent being converted into benzenesulfinic acid and nitrogen. Other applications of tosyl hydrazide include a procedure to make sulfones with halides with the evolution of nitrogen[2a] and as a precursor for diazene.[2b] Acyl derivatives are frequently required and can now be prepared with high regioselectivity.[3] Fukuyama et al. were able to trap the nitrogen originating from the reaction of 1,2-ditosylhydrazine (**1**) with bromoacetates in the presence of DBU with the formation of diazoacetates.[4] An α-bromomethylketone also furnished the corresponding diazoketone.

Prompted by the work of Rasmussen,[5] and in continuation of our earlier work on tosyl hydrazides,[6] we made an attempt to benzylate **1** and obtained a mixture of two components that could be resolved easily by chromatography. The major component proved to be benzyl 4-methylphenylsulfone (**2**, Ts–Bn[7]), identified without comments by Rooney et al. as a minor product in the reaction between BnCl and tosyl hydrazide.[8] Following chromatography on silica gel with dichloromethane we obtained minor amounts of the previously described hydrazone **3** (Table 1, entry 1a).[9] Inspection of the literature indicated that formation of hydrazones such as **3** had not been described under similar conditions, and because of a contradictory claim discussed below, we decided to explore the reaction further to rationalize our findings.

The original experiment was performed under mild conditions similar to those described by Rasmussen.[5] Thus, a solution of **1** in DMF in the presence of two moles of Cs_2CO_3 was reacted with BnBr in slight excess (Scheme 1). The addition of Cs_2CO_3 to the hydrazine solution was accompanied by slight gas evolution for more than an hour. This initially overlooked observation led us to perform a series of experiments based on preincubation with base for various periods of time before BnBr was added, the outcome of which could easily be determined because products **2** and **3** are both highly crystalline (Table 1).

As demonstrated in entries 1b–1h, the design of these experiments had a drastic effect on the product distribution which could be monitored conveniently from the benzyl signals of the crude products. Under appropriate conditions and with enough Cs_2CO_3, sulfone **2** was formed exclusively and quite rapidly in essentially quantitative yield, whereas after only short preincubation, variable amounts of the hydrazone **3** were also obtained. With lesser base, a considerable amount of starting material **1** remained. Without preincubation, a maximum yield of 50% of pure **3** was obtained.

As Rasmussen's work demonstrated a unique effect of cesium compared to potassium carbonate on alkylation of hydrazines, we also conducted experiments with anhydrous potassium and sodium carbonate with comparable results (entries 2 and 3). Further benzylation experiments were carried out with triethylamine and 1,1,3,3-tetramethylguanidine (TMG) as base. Triethylamine in DMF was also found to initiate conversion into **2**, although obviously much more slowly and less completely than in the previous experiments as demonstrated by the presence of unreacted **1**, but

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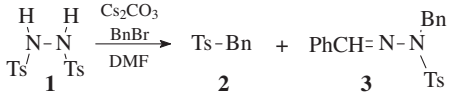
Table 1
Attempted benzylation experiments with **1**

Entry	Base[a]	Reagent ratio[b]	Preincubation/reaction time (h)	Yield[c]	Other products (%)
1a	A	1:2:2.2	—/2	0.106/59[d]	17[d] (**3**)
1b	A	1:2:2.2	24/2	0/92	—
1c	A	1:2:2.2	3/0.5	<0.003/93	—
1d	A	1:2:2.2	0.2/2	0.158/58[d]	27[d] (**3**)
1e	A	1:2:2.2	0/2	0.470/45[d]	50[d] (**3**)
1f	A	1:1:2.2	3/0.5	0.013/83	—
1g	A	1:0.5:2.2	3/0.5	<0.001/38	40 (**1**)
1h	A	1:1:1.1	24/2	0/52	—
2	B	1:2:2.2	24/2	0/92	—
3	C	1:2:2.2	24/2	<0.003/92	—
4a	D	1:2:2.2	24/2	<0.005/49[d]	<1 (**3**); 22 (**1**)
4b	D	1:2:2.2	0.1/2	0.348/23[d]	15[d] (**3**); 42 (**1**)
5	E	1:2:2.2	0.2/2	0/89	—
6	F	1:2:2.2	0.2/2	0/88	—
7a	G	1:2:2.2	3/0.5	0/92	—
7b	G	1:2:1.1	3/0.5	0/48	—
7c	G	1:1:1.1	0.2/0.5	0/45[e]	55[e] (**1**)
7d	G	1:1:1	1/0.5	0/50[e]	50[e] (**1**)

[a] Bases are abbreviated: A = Cs_2CO_3, B = K_2CO_3, C = Na_2CO_3, D = Et_3N, E = TMG, F = TMG + DMSO, G = KO^{t}Bu.
[b] All experiments were performed with 1 mmol of **1** in 4 mL of DMF (except 6); compound **1**: base: BnBr molar ratio.
[c] Crude product 4.85/4.29 ppm ($CDCl_3$) or 5.00/4.62 ppm [$(CD_3)_2SO$] proton signal ratio/yield of recrystallized **2** (%).
[d] After chromatography and crystallization.
[e] By NMR spectroscopy.



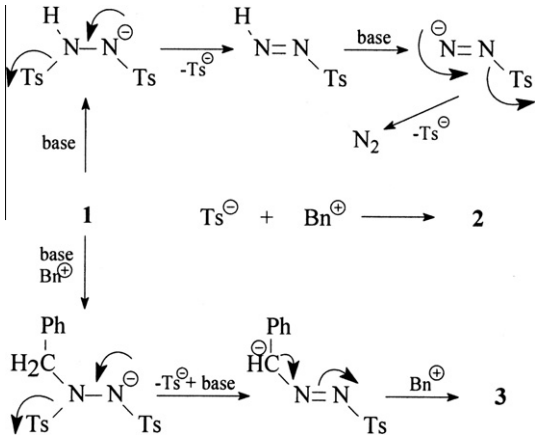
Scheme 1. Initial attempt at benzylation of **1**.

still testifying to the instability of **1** to bases. Interestingly, TMG immediately gave rapid nitrogen evolution lasting for about 5 min, quickly allowing benzylation to be initiated, and furnished **2** in essentially quantitative yield. Identical results were obtained with this base in DMSO instead of DMF. Thus, with TMG the preincubation time required for complete conversion of **1** into **2** could be significantly reduced (entries 5 and 6).

The use of TMG as a base provided a simple method to monitor directly the preincubation step in DMSO by ^{1}H NMR spectroscopy. In this way it could be demonstrated that a 0.1 M solution of **1** with 2.5 equiv of TMG at room temperature had, within about 25 min, been completely converted into the TMG salt of the corresponding sulfinic acid, 4-CH_3–C_6H_4–SO_2H. Furthermore, by monitoring relevant signals every two minutes and fitting the data to a second order reaction equation, the half-life of **1** was calculated to be less than 1.5 min (for more details see Supplementary data). This reactivity to base seems to be unique for a compound of the present type. The sulfinate solution appeared to be stable for several weeks.

Sulfinate salts are ambient nucleophiles that undergo alkylation on sulfur and they are therefore useful precursors of sulfones.[10] Fukuyama et al. found small amounts of a by-product (<5%) on treatment of **1** with an excess of DBU in THF at 0 °C which was characterized as a sulfone.[4] A reasonable rationale for the formation of **2** is that deprotonation of **1** by the base initiates an elimination reaction with the generation of sulfinate and eventual extrusion of nitrogen, the rate of which varies with the strength of the base. If BnBr is added before this step is completed, competing N-benzylation takes place. Subsequent elimination of one tosyl as a sulfinate leads to partly oxidized product **3**, otherwise a remarkably smooth and clean S-benzylation occurs. Mechanistic studies on substrates for the McFadyen–Stevens reaction[11] of the 1-benzenesulfonyl-2-benzoyl-hydrazine type have been published.[12] By analogy, a postulated mechanism for the formation of **2**, featuring complete reduction of the tosyl and nitrogen formation via an intermediate of the tosyldiazene type is depicted in Scheme 2. Interestingly, the authors claimed they could treat a DMSO solution of **1** with NaOD/D_2O and reverse its effect with HCl and also noted that sodium ethoxide gave rise to sodium *p*-toluenesulfinate on standing.[12] It has also been stated that **1** is soluble in aqueous sodium hydroxide and the author concluded that this would prove the position of the tosyl groups.[13]

Wessig and Henning have reported the reaction of **1** with 1 equiv each of KO^{t}Bu and BnBr in DMF and obtained the monobenzyl derivative, Ts(Bn)N–NHTs, in a 70% yield.[14] Since this claim would disprove our findings about the effect of bases, including even much weaker ones, on **1**, we decided to perform a few experiments with **1** and KO^{t}Bu under similar conditions (entries 7a–d). As with TMG, in our hands, KO^{t}Bu gave instant nitrogen evolution and furnished, after preincubation, exclusively **2** in a 92% yield (with 2.2 equiv of BnBr) and a 48% yield (with 1.1 equiv of BnBr), respectively, in the presence of 2 equiv of base. On the contrary, with only 1 equiv of this base, 50–55% of the starting material remained together with **2** at the end of the reaction. From a mechanistic point of view this implies that the postulated intermediate above, HN=N–Ts, is deprotonated preferentially to **1** when the



Scheme 2. Postulated mechanism for the formation of **2** and **3**.

Table 2
Substrate stability of 1-X^1-2-X^2-hydrazides toward TMG

Entry	X	X^1	X^2	Product:substrate ratio/time[a] (selected data)	Estimated half-life[b]
1	**4**	Ts	H	0.76/1.8; 1.48/8.7	4
2	**5**	Ts	Boc	0.86/171; 1.20/219	190
3	**6**	Ts	Z	0.94/227; 1.15/266	240
4	**7**	Ts + Boc	H	See discussion in the text	n.d.
5	**1**	Ts	Ts	For details, see Supplementary data	<1.5 min

[a] 0.1 mmol Substrate in $(CD_3)_2SO$ (ca. 590 μL) + 1.25 equiv TMG at RT; measured (always Ts–Me, in several cases also aromatic Ts signals) sulfinate product: substrate ratio by ^1H NMR spectroscopy/days.
[b] Days (by linear interpolation).

supply of base is limited. As no product other than **2** could be isolated in these experiments we conclude that the claim of Wessig and Henning is not correct.

Ts-$NHNH_2$ Ts-NHNH-Boc Ts-NHNH-Z

4 **5** **6**

In the initially mentioned method to prepare sulfones,[2a] the authors reacted tosyl hydrazide (**4**) and alkyl or activated aryl halides in boiling ethanol with sodium acetate as the base. The reaction required an excess of halide and base and typical reaction times of 3–24 h to go to completion. Interestingly, the authors claimed that in addition to tosyl, some of the halides were also reduced. For comparison with **1**, we investigated the stability of **4** toward TMG in DMSO (Table 2, entry 1) and found that it also decomposed into sulfinate, exclusively, but with a half-life of a few days instead of minutes, suggesting **1** as a more reactive, much milder alternative to **4** in this context. It should be pointed out that a large number of sulfonyl analogs of **1** have also been described.[15]

Introduction of a Boc-group on tosyl hydrazide-N^2 **5** had an opposite effect in comparison with that of a second tosyl. Compound **5**[16a] only reacted very slowly to give a sulfinate (entry 2). This result was corroborated for its Z-analog **6**[16b] which exhibited similar reactivity (entry 3). In these measurements with **5** and **6**, over several months, the observed chemical shifts drifted to a variable degree toward lower field, least for Ts–Me, and most for the Ts-3,5-proton signals (±0.008 and 0.028 ppm, respectively), but the conversions into sulfinate seemed to take place without detectable intermediates and were completely selective.

Ts-NNH_2 (Boc) Ts-NNH_2 (CO-N=C(NMe_2)NMe_2)

7 **8**

Interestingly, substrate **7**[16c] with a Boc-group on the tosyl hydrazide-N^1 reacted rather differently with TMG than the other compounds studied in Table 2 (entry 4). After about two days the substrate was no longer detectable and at least two products had formed. The major product was isolated from a small-scale preparative experiment (for details see Supplementary data). Based on spectroscopic data it was tentatively assigned a structure of a semicarbazide that had incorporated TMG, Ts–N(NH_2)–CO–TMG (**8**), formally by substitution on the Boc-carbonyl group. It remains to be demonstrated that similar compounds can be made in the same way.

The half-lives of the other compounds as determined in Table 2 together with **1** span a range of more than 5 orders of magnitude, of which 3–3.5 refer to the introduction of the second tosyl group. The dramatic behavior of **1** toward bases as reflected in Table 1 and illustrated visually by the evolution of nitrogen as described above are interesting in this perspective.

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Supplementary data

Supplementary data (starting materials and synthetic procedures used, NMR and HRMS spectral data, primary kinetic data for **1**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.061.

References and notes

1. For a recent summary on applications of tosyl hydrazide, see: Chamberlin, A. R., ; Sheppeck, J. E., II; Goess, B.; Lee, C. In Paquette, L. A., Crich, D., Fuchs, P. L., Molander, G. A., Eds.; Encyclopedia of Reagents for Organic Synthesis; Chichester: Wiley, 2009; 12, pp 9634–9645. 2nd ed.
2. (a) Ballini, R.; Marcantoni, E.; Petrini, M. *Tetrahedron* **1989**, *45*, 6791; (b) Pasto, D. J.; Taylor, R. T. *Org. React.* **1991**, *40*, 91.
3. Namba, K.; Shoji, I.; Nishizawa, M.; Tanino, K. *Org. Lett.* **2009**, *11*, 4970. and references therein.
4. Toma, T.; Shimokawa, J.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 3195.
5. Rasmussen, L. K. *J. Org. Chem.* **2006**, *71*, 3627.
6. (a) Ragnarsson, U.; Grehn, L.; Koppel, J.; Loog, O.; Tšubrik, O.; Bredikhin, A.; Mäeorg, U.; Koppel, I. *J. Org. Chem.* **2005**, *70*, 5916. and references therein; (b) Ragnarsson, U. *Chem. Soc. Rev.* **2001**, *30*, 205.
7. It should be pointed out that for the sake of simplicity in this Letter Ts is used as an abbreviation for 4-$CH_3C_6H_4SO_2$ independent of its state of oxidation or charge.
8. Rooney, C. S.; Cragoe, E. J., Jr.; Porter, C. C.; Sprauge, J. M. *J. Med. Pharm. Chem.* **1962**, *5*, 155.
9. Keith, J. M.; Gomez, L. *J. Org. Chem.* **2006**, *71*, 7113.
10. See for example: Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon Press: Oxford, 1993.
11. Mosettig, E. *Org. React.* **1954**, *8*, 232.
12. Matin, S. B.; Craig, J. C.; Chan, R. P. K. *J. Org. Chem.* **1974**, *39*, 2285.
13. Jennings, K. F. *J. Chem. Soc.* **1957**, 1172.
14. Wessig, P.; Henning, H.-G. *Liebigs Ann. Chem.* **1991**, 983.
15. Bartmann, E. A. *Synthesis* **1993**, 490.
16. (a) Ragnarsson, U.; Grehn, L.; Maia, H. L. S.; Monteiro, L. S. *J. Chem. Res.* **2000**, (S) 6; (M) 129.; (b) Grehn, L.; Nyasse, B.; Ragnarsson, U. *Synthesis* **1997**, 1429; (c) Grehn, L.; Ragnarsson, U. *Tetrahedron* **1999**, *55*, 4843.