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An unprecedented rearrangement of a 1,1-diprotected hydrazine derivative. Structure revision of a catalyst-containing by-product

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ABSTRACT

Treatment of 1-Boc-1-tosyl-hydrazine with 1,1,3,3-tetramethylguanidine (TMG) gave rise to two products, one containing and the other not containing TMG. The latter was identified as 1-Boc-2-tosyl-hydrazine. This rearrangement provided useful insight into the nature of the first product that had previously been isolated and assigned an incorrect tentative structure. To rationalize the results a plausible mechanism via a common intermediate, involving TMG as a nucleophilic catalyst is proposed. A simpler procedure for the preparation of the starting material is also presented.

The stability of aromatic sulfonamides to acids and bases and their sensitivity to reducing agents is the basis for the application of tosyl (Ts) and related groups for the protection of amino functions.[1] Similarly, *tert*-butyl carbamates generally exhibit high base stability, but undergo cleavage by acids, a protection strategy that is nowadays well established in synthetic work involving amines. *tert*-Butyl sulfonylcarbamates with both types of group on the same amino function can often be made and exploited to improve the stability and selectivity further.[2,3] Sulfonylhydrazines exhibit a rather different stability profile from sulfonamides and undergo intramolecular redox reactions, and this property was exploited a long time ago for the thermal decomposition of acylbenzenesulfonylhydrazines in the classical McFadyen–Stevens aldehyde reaction.[4]

In connection with attempts to alkylate 1,2-ditosylhydrazine, we became intrigued by its extreme sensitivity to cleavage by a base to form a sulfinate and nitrogen. In some experiments the evolution of the latter became so intense that it could be observed with the naked eye.[5] Monitoring the formation of the sulfinate by ^{1}H NMR spectroscopy, we demonstrated that with 1,1,3,3-tetramethylguanidine (TMG) as the base in DMSO, the reaction took place with a half-life below two minutes. Nevertheless, Fukuyama and co-workers. recently succeeded in preventing the decomposition of the substance and in trapping the nitrogen with bromoacetates to form diazoacetates.[6] In our previous paper, we also studied the reaction of a few monotosyl hydrazine derivatives with TMG, and with Ts(Boc)NNH$_2$ we isolated a novel TMG-containing product that was assigned a tentative structure.[5] More recent work in our laboratory has resulted in the discovery that Ts(Boc)NNH$_2$ can undergo an unprecedented rearrangement, and as a consequence of this, to the revision of the previously described structure. In the present Letter additional experiments are reported with the objective to shed light on this unusual reaction.

A short summary of relevant previous results

For comparison with 1,2-ditosylhydrazine, sulfinate formation in the presence of TMG (1.25 equiv) of four monotosylated hydrazine derivatives, Ts-NHNH$_2$ (**1**), Ts-NHNH-Boc (**2**), Ts-NHNH-Z (**3**), and the above-mentioned Ts(Boc)NNH$_2$ (**4**), was monitored by ^{1}H NMR spectroscopy in DMSO-d_6 at room temperature. Compounds **1**–**3** were selectively cleaved, although with half-lives of a few days for **1** and several months for **2** and **3**. Part of the sulfinate was thereby converted into a sulfonate.[7,8] Compound **4** behaved differently from the others and there was an obvious mismatch between its disappearance and the slow formation of a sulfinate.

Based on two NMR experiments with **4**, one of which was monitored over several weeks and the other more frequently up to two weeks, we noticed that it had reacted completely within about two days, essentially with formation of two products in addition to the sulfinate/sulfonate. Although our interest was initially focused on the stability of the tosyl group, in particular the appearance of a prominent singlet at 2.55 ppm aroused our interest, and in a

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small-scale preparative experiment, a solid hydrazine derivative containing TMG, $C_{13}H_{21}N_5O_3S$, was isolated in modest yield. This seemed to be the major and most interesting product, whereas the other was obtained in a minor amount as an impure viscous oil and was not characterized. The solid was assigned the tentative structure, Ts-N(NH_2)-CO-NC(NMe_2)$_2$, with a tetramethylguanidinocarbamoyl group attached to the tosyl nitrogen, referred to as the catalyst-containing by-product in the title of this Letter.

A missing link and small scale preparative experiments

We have now studied further the unusual reactivity of **4** in the presence of TMG. To start with we carried out an experiment with 1.25 equiv of TMG on a 5 mmol scale as described in the Supplementary material, and obtained a correspondingly larger amount of the TMG-containing material **5**, as a completely stable, crystalline solid with all the spectral characteristics in agreement with those given earlier.[5] However, from the mother liquor, it was possible to isolate another pure solid that was identified as Ts-NHNH-Boc[9] (**2**), indicating that a rearrangement of the starting material had taken place under the influence of the strong base. This observation provided a link to the nature of the first product that was previously missing. In this Letter its structure has been revised (compound **5** in Scheme 2).

The outcomes of varying the reaction time and temperature and the amount of TMG used were studied, first in DMSO and then in DMF, as detailed in Table 1. In both solvents at room temperature the two products were formed, but in varying relative proportions. In all cases the TMG-containing species was found to be the major product, particularly so in entries 5 and 7. These experiments and that at 50 °C indicated that the product ratio was strongly temperature dependent. A small excess of TMG was required for complete conversion of the substrate in DMSO within 2–3 days, but further amounts seemed to have a negative effect on the total yield, suggesting that a side-reaction had taken place. This could be due to the increased formation of the sulfinate/sulfonate. However, these experiments did not provide conditions for a clean rearrangement of compound **4** into **2**.

Spectral studies

Studies on compound 4

Figure 1 presents the proton spectrum of compound **4** (100 μmol) after the reaction with TMG (125 μmol) in 0.6 mL of DMSO for 30 h at room temperature. In the Ts-Me region (2.41–2.28 ppm) the signal belonging to **4** at 2.41 ppm was the largest, indicating that about 42% still remained, whereas those of **5** at 2.35 ppm amounted to 33% and **2** at 2.32 ppm to 22% and sulfinate/sulfonate to less than 4%. The prominent singlet at 2.55 ppm mentioned earlier integrates for 4 times the number of protons compared to those at 2.35 ppm. Among the three major sets of aromatic doublets, that belonging to **4** at 7.81/7.43 ppm also corresponds to 42% and those of **5** at 7.68/7.29 ppm to 34% and **2** at 7.60/7.21 ppm to 20%. The latter signals were significantly broadened. Similarly, the remaining strong singlets at 1.30 and 1.12 ppm correspond to about 43% and 42%, respectively, of the total number of *tert*-butyl protons present, whereas the very broad signal at 1.22 ppm integrates for about 15%.

A comparison with the spectral data for pure **5** and **2** reveals upfield changes in the shifts of the Ts-3,5-protons at 0.03 and 0.15 ppm, respectively, in the presence of TMG. Of the Ts-Me signals, only that of **2** undergoes a 0.05 ppm shift, also upfield. Together with the observed broad signals, this indicates that **2** interacts strongly with TMG in DMSO.

Surprisingly, inspecting the spectrum of the same sample after 50 h demonstrated that all the signals originating from **4** were completely missing. Moreover, the 2.35/2.32 signal ratio had increased from 1.5 to about 2.6. Further monitoring of the reaction gave rise to a similar spectrum after 74 h, although the amount of sulfinate/sulfonate formed was estimated to be about 8%; both spectra are reproduced in the Supplementary material. Another spectrum from a different experiment after 22.5 h resulted in figures similar to those presented in the preceding paragraph. In this case 54% of **4** still remained.

Studies on compounds 2 and 5

Authentic compound **2** in the presence of a small excess (1.25 equiv) of TMG in DMSO is rather stable[5] and exhibits the spectral characteristics found in mixtures with **5** in the preceding section, such as the strong upfield shift of its Ts-Me and very broad Boc-Me signals. As compound **2** in this solvent has a pK_a of 14.5[10] compared to 13.2 for $TMGH^+$,[11] this is obviously due to partial deprotonation. Initial sulfinate/sulfonate formation is about 1%/day, which in reactions involving **2** should progressively increase the protonation of TMG and lead to reduced upfield shifts.

Authentic compound **5** was also studied under the same conditions and was found to give rise to sulfinate/sulfonate formation at an initial rate about 10 times faster than **2**. This value is higher than that found in connection with the monitored reaction of **4** discussed above.

Table 1
Small scale experiments with compound **4** and TMG

Entry	TMG (equiv)	Time (d)	Solvent	Yield[a] (mg)	Ratio **5**/**2**[b]	Comments[c]
1	1	2	DMSO	134[d]	1.62	RT
2	1.25	3	DMSO	141	1.85	RT
Prep[e]	1.25	3	DMSO	940	2.12	5 mmol, RT
3	2	2	DMSO	100	3.32	RT
4	0.5	1	DMSO	121[f]	1.43	50 °C
5	1.25	3	DMF	107	7.70	RT
6	1.25	3	DMF	107[g]	0.99	50 °C
7	1.25	5	DMF	93	>10	4 °C
8	1.25	6	DMF	>95% of **4**	n.d.	−18 °C
9	2	3	DMF	69	2.74	RT
10	2	7	DMF	68	2.13	RT

[a] Yield of crude solid material.
[b] Proton signal ratio at 2.36/2.375 ppm in DMSO-d_6.
[c] Syntheses generally performed on a 0.5 mmol scale.
[d] Contained 19% of starting material **4**.
[e] Preparative experiment, described in Supplementary material.
[f] Contained 47% of starting material **4**.
[g] Contained DMF.

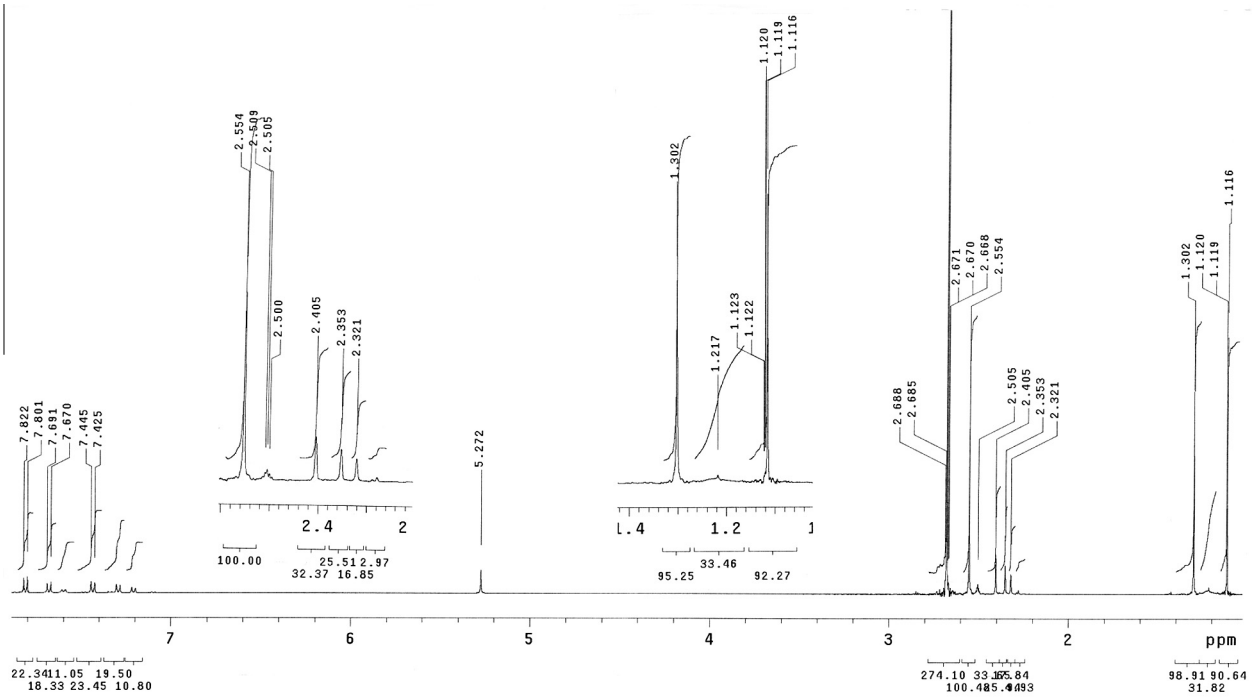


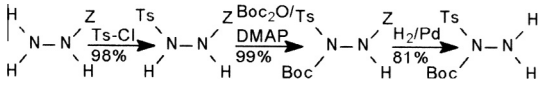
Figure 1. Proton spectrum (400 MHz) of compound **4** (28.6 mg, 0.1 mmol) after reaction with TMG (1.25 equiv) in DMSO-d_6 (0.6 mL) for 30 h at RT.

The revised structure of the TMG-containing product

The fact that compound **4** in the presence of TMG partly rearranges into **2** encouraged us to reconsider the structure of our previously isolated TMG-containing product **5**, since the two compounds are apparently formed competitively. The presence of two unequal low field protons in **5**, as in **2**, together with intact TMG and tosyl moieties, the ^{13}C NMR spectral data, and the previously presented HRMS spectrum[5] confirm the structure of this compound as 2-[(1′,1′,3′,3′-tetramethylguanidino)-carbamoyl]-1-tosylhydrazine instead of the 1-[(1′,1′,3′,3′-tetramethylguanidino)-carbamoyl] structure tentatively given.

Synthesis of Ts(Boc)NNH$_2$ directly from 1

Originally, compound **4** was prepared from Z-NHNH$_2$ in three simple steps in an overall yield of 79% as described in Scheme 1.[12] More recently, Namba et al. demonstrated that an N^1-acyl-N^1-Ts-hydrazine derivative could be prepared with high selectivity directly from Ts-NHNH$_2$ with various acylating reagents and catalytic amounts of 4-aminopyridine or DMAP in the presence of an excess of triethylamine.[13] Considering the fact that **4** can be crystallized easily from cold ether, we decided to use Namba's reaction conditions with Boc$_2$O instead. The result turned out to be highly satisfactory and small amounts of by-products could be removed this way. That the sulfonamide function of Ts-NHNH$_2$ in the presence of DMAP reacts with Boc$_2$O in preference over the N-NH$_2$ group is a further illustration of the observation by Bordwell and co-workers that the reaction rate increases with the acidity of the substrate.[14] The requirement for a base (triethylamine) strongly indicates that sulfonamide anion acts as the nucleophile.



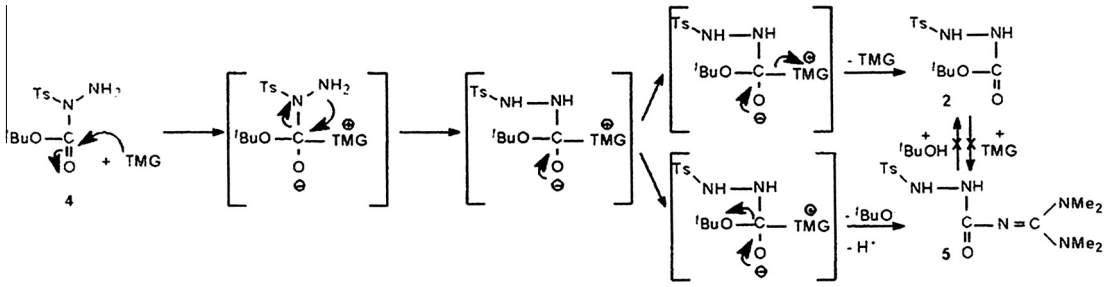
Scheme 1. Original synthesis of Ts(Boc)NNH$_2$.

Postulated mechanism for the rearrangement of 4 into 2 in the presence of TMG as well as for the formation of 5

Compound **4** with two electron-withdrawing groups on the same nitrogen obviously exhibits low electron density at this site, which should affect its overall basicity dramatically. In DMSO it even behaves as a weak acid with a pK_a of 15.9,[10] and with a value for TMGH$^+$ nearly three orders of magnitude lower it can therefore be expected to be only marginally sensitive to deprotonation by TMG. In contrast to **2**, it does not exhibit significant changes in its chemical shifts in the presence of this base. An analogous compound was characterized as a nonbasic amine maintaining its nucleophilicity.[13]

Our spectral studies of the reaction of compound **4** with TMG established that most of the *tert*-butyl groups originally present in the Boc-functions were converted into *tert*-butanol as judged from the signal at 1.12 ppm.[15] This indicates that **4** underwent major CO–O^{t}Bu bond cleavage in connection with its rearrangement, that we propose is initiated by nucleophilic attack of the catalyst at the sulfonylcarbamate carbonyl center with formation of a more reactive tetrahedral pre-transition state complex. Direct deprotonation is believed to be insignificant in this case and requires a stronger Brønsted base than TMG. This complex is then postulated to undergo an intramolecular nucleophilic N^1 to N^2 shift via a corresponding tetrahedral transition state that can lead to the two products **2** and **5** by elimination of either TMG or butoxide. As demonstrated in Table 1, the outcome of the final step is obviously strongly dependent on the reaction temperature and solvents and less so on stoichiometry and reaction time, although occasionally is somewhat blurred by accompanying tosyl cleavage. In this context attention should be given to the pioneering work by Namba et al. dealing with bromohydrazidation of β,γ-unsaturated *N*-acyl-*N*-tosylhydrazines,[16] in which the terminal amino group also reacts as a nucleophile intramolecularly similar to that which we postulate in the rearrangement of compound 4.

Scheme 2 highlights the role of TMG as a catalyst in the intramolecular transfer of the Boc-group from the substrate to



Scheme 2. Postulated rearrangement and substitution mechanism.

Table 2
Direct synthesis of Ts(Boc)NNH_2 with Boc_2O and DMAP from Ts-$NHNH_2$ in the presence of Et_3N

Entry	Reagent ratio[a]	Temp (°C)	Yield (%)
1	1:1.05:1.5:0.1	2	75
2	1:1.05:1.5:0.05	2	71
3	1:1.05:1.2:0.05	RT	70 + 10[b]

[a] Ts-$NHNH_2$/Boc_2O/Et_3N/DMAP molar ratio; all syntheses performed on a 10 mmol scale.
[b] Recovered from the mother liquor, see Supplementary material.

the product **2**. Its action as a nucleophile is understood to favor energetically nucleophilic attack by the substrate amino function leading to the rearrangement. Competing elimination of *tert*-butoxide at the transition state then results in the irreversible formation of compound **5** as a by-product. Previous work (experiment 2 of Table 2[5]) allows us to conclude that compound **2** cannot be converted into **5** with TMG. We have also verified that in the presence of *tert*-butanol the reverse reaction does not take place.

Retrospective considerations and conclusions

Alkylation of hydrazine derivatives is not always straightforward and can provide surprises.[17] In the initially mentioned unsuccessful experiment with Ts-NHNH-Ts, its strong inherent reduction ability in the presence of the base gave rise to exceptional tosyl cleavage. The extension of this work to include other substrates such as compound **4** and other bases like the superbase TMG led to the isolation of the TMG-containing product. It became something of a marker in the present work that resulted in the discovery of a novel rearrangement, in which TMG played the role of a catalyst. From a formal point of view this is an acyl transfer reaction.

The extended work reported above has shed light on the reaction leading to the anticipated TMG-containing product. Its structure has been revised and a plausible mechanism for its formation is presented, linked to another rearranged product. We therefore conclude that the objective of the project has been met. Besides, a simpler method for the preparation of substrate **4** has been presented.

Experimental

See Supplementary material.

Acknowledgments

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Supplementary material

Supplementary data (two proton spectra related to Figure 1 and synthetic details related to Tables 1 and 2 and compounds **2**, **4** and **5**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.121.

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