Multisubstituted Urea Derivatives of Hydrazines by a Flexible Approach with Potential Application in Combinatorial Chemistry

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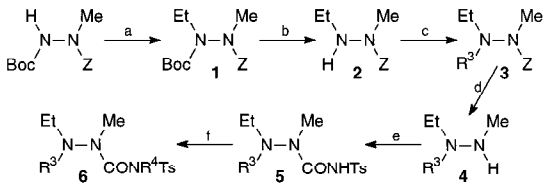
Abstract: Using inexpensive, readily available starting materials, a trisubstituted hydrazine was synthesized by our recently developed techniques and converted to the corresponding tosylcarbamoyl derivative (*N*-tosylsemicarbazide) which can be further alkylated on its carbamoyl nitrogen under Mitsunobu conditions to give compounds of type **6**. The yields in all steps are high. Similarly, selectively protected, *N,N'*-substituted hydrazines can be tosylcarbamoylated twice with intermediary alkylation to give dimeric ureas **11** with four different substituents in addition to the tosyl groups. The latter can in principle be replaced by other sulfonyl groups of higher pharmaceutical interest, thus allowing simultaneous variation of 5 sites in **6** or 6 such in **11**. Due to the importance of ureas and sulfonylureas as pharmaceuticals, these new flexible synthetic schemes might therefore be applicable in the search for new lead substances by combinatorial chemistry. In connection with this work an unprecedented *N*-benzyl cleavage by trifluoroacetic acid of potential practical interest was discovered.

Key words: combinatorial chemistry, multisubstituted hydrazines, 1,2-bis(tosylcarbamoyl)hydrazines, Mitsunobu substrate, ureas

Combinatorial chemistry, which attempts to synthesize large numbers of new compounds by condensing a small number of reagents together in many, if not all possible combinations, is nowadays in high demand for the generation and optimization of lead compounds for new drugs.[1] It can be achieved in many different ways, such as in mixtures to produce libraries or in large numbers of parallel vessels either on a solid support[2a,b] or in solution.[2c] Clean basic chemistry is as usual a prerequisite for success in work involving multistep schemes. The earliest work in the combinatorial chemistry field dealt with peptides.

Until recently relatively little work was reported on selective substitution of hydrazine and preparation of unsymmetrical hydrazine derivatives.[3] Using modern protective groups we made a couple of triprotected hydrazine reagents which allowed rational stepwise alkylation and acylation to be performed.[4] In this paper we describe further work with di- and trisubstituted hydrazine derivatives as starting materials for the preparation of multisubstituted ureas. Two flexible schemes are presented, both allowing preparation of such compounds under experimentally simple, carefully controlled conditions in high yield and purity on a laboratory scale.

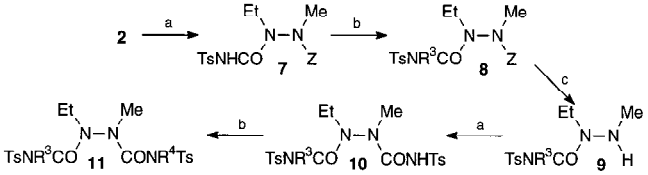
For the synthesis of the maximally substituted semicarbazide model compound **6** (Scheme 1) we chose the readily available 2-Boc-1-methyl-1-Z-hydrazine[4c] as the starting material, which could be alkylated under the previously described phase-transfer catalysis (PTC) conditions, and isolated **1** as a crystalline material in nearly quantitative yield. Removal of the Boc group from this orthogonally protected intermediate furnished **2** as an oil which was acylated to afford again a crystalline substance **3**. Catalytic hydrogenolysis gave **4** as an oil. This was reacted with tosyl isocyanate and the product **5** isolated by crystallization. Since this intermediate contains an acidic sulfonylurea proton, we made an attempt to alkylate it with an alcohol under Mitsunobu conditions[5] and, indeed, succeeded in isolating **6** as an oil in fair yield. At this stage chromatographic workup was required. Weinreb et al.[6] first reported the alkylation of sulfonamides under these conditions, but obviously *N*-tosylureas also undergo this reaction. To the best of our knowledge compound **6** is the first pentasubstituted semicarbazide prepared so far.



Z = C(O)OBn, **3–6**: R^3 = 4-FC_6H_4CO, **6**: R^4 = $Ph(CH_2)_4$. (a) EtI, PTC conditions (98%); (b) TFA (99%); (c) R^3Cl (93%); (d) H_2/Pd; (e) TsNCO (97% from **3**); (f) R^4OH (Mitsunobu conditions) (61%).

Scheme 1

Having accomplished the synthesis of **6**, we reacted compound **2** with tosyl isocyanate and obtained **7** (Scheme 2) by analogy with **5** as a crystalline solid. This intermediate was alkylated with two different alcohols under Mitsunobu conditions to give **8a** and **8b** as oils in 79 and 59% yield after purification by chromatography. The former intermediate was hydrogenolyzed catalytically and the oily **9** reacted a second time with tosyl isocyanate producing, again, a crystalline solid product **10** in nearly quantitative yield. From this compound we could obtain the desired final product **11** by a Mitsunobu alkylation under the conditions used for **6** and **8** above. The product **11** is be-



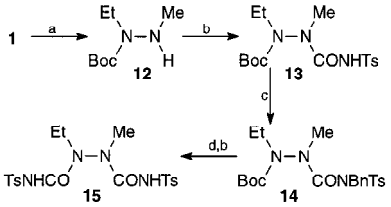
8a–11: R^3 = CD_3, **8b**: R^3 = Me_2CHCH_2, **11**: R^4 = Bn. (a) TsNCO (**7**: 99%; **10**: 95% from **8a**); (b) R^3OH/R^4OH (Mitsunobu conditions) (**8a,b** 59–79%; **11**: 79%); (c) H_2/Pd (97%).

Scheme 2

lieved to be the first hexasubstituted dimeric urea (carbazide) of its kind, carrying the maximally conceivable number of non-hydrogen substituents on its nitrogens and exploiting the hydrazine moiety as a scaffold exhaustively. Together with **6** it attests to the usefulness of the selectively protected difunctional reagent used as starting material.[4c] The latter features dual protection of one of the hydrazine nitrogen atoms,[7] as a result of which side reactions are efficiently minimized at this site.

In addition to previously available procedures for the preparation of unsymmetrical ureas,[8a] several new, flexible ones have recently been developed.[8b–f] Although several sulfonylureas are commercially important as antidiabetic agents and can be prepared from sulfonamides and isocyanates,[9] few alkylated sulfonylureas have been described in the literature. The present procedure, involving alkylation under Mitsunobu conditions, might occasionally be an attractive alternative, when the alcohol is available, although the yields seem to be significantly lower for tosylureas than for tosylcarbamates.[10] In all other individual steps involved in the synthesis of our model compounds yields were generally nearly quantitative and Schemes like 1 and 2 might therefore be applicable in combinatorial chemistry for the synthesis of small focused urea and/or sulfonylurea libraries.[11] Furthermore, since many compounds containing such groups are highly crystalline and easy to purify, individual components of high purity should result from parallel synthesis.

Finally, we should like to briefly mention an unexpected side reaction encountered in connection with Scheme 2. In an attempt to prepare another derivative of **11**, starting from **1** (Scheme 3), we first performed a hydrogenolysis and then reacted the intermediate **12** with tosyl isocyanate and obtained **13**. Mitsunobu alkylation with benzyl alcohol also provided the expected product **14**, but this turned out to be labile to the trifluoroacetic acid used to cleave off the Boc group and therefore compound **15** without the *N*-benzyl group was formed in the subsequent reaction with tosyl isocyanate. We interpret this cleavage to be a consequence of an exceptionally low electron density on the benzyl nitrogen which favored the release of a benzyl carbenium ion from the protonated species.



(a) H_2/Pd (89%); (b) TsNCO (**13** 97%); (c) BnOH (Mitsunobu conditions (79%); (d) TFA (**15** 80%).

Scheme 3

The general experimental conditions agreed with those earlier reported.[4c] TLC systems were: (A) toluene/MeCN 2:1; (B) light petroleum (bp 40–65 °C)/Et_2O 2:1; and (C) CH_2Cl_2/acetone/HOAc 40:10:1.

1-(Benzyloxycarbonyl)-2-(*tert*-butoxycarbonyl)-2-ethyl-1-methylhydrazine (1):

To a solution of 2-Boc-1-Me-1-Z-hydrazine[4c] (2.80 g, 10.0 mmol) in anhyd benzene (40 mL) was added Bu_4NHSO_4 (0.68 g, 2.0 mmol), finely ground, dried K_2CO_3 (4.14 g, 30 mmol) and freshly ground NaOH (1.20 g, 30 mmol) under argon at r.t. The resulting slurry was vigorously stirred for a few minutes, whereafter neat EtI (4.78 g, 30 mmol) was introduced dropwise with rapid stirring over a period of 30 min. The reaction was then allowed to further proceed under the above conditions with monitoring by TLC (B). After 30 h, no remaining starting material could be detected and most of the solvent was removed at reduced pressure. The semisolid residue was partitioned between Et_2O (300 mL) and aq 1 M $KHSO_4$ (150 mL) and the organic extract was washed in turn with 1 M $KHSO_4$, 1 M $NaHCO_3$ and brine (3×75 mL each) and dried ($MgSO_4$) in the presence of decolorizing carbon. Removal of the solvent left a colorless viscous oil which soon solidified. The yield of crude, chromatographically pure (A, B) **1** was 3.02 g (98%) after thorough drying under high vacuum. Recrystallization from light petroleum (15 mL/g, decolorizing carbon) provided white, soft needles after 24 h at –20 °C; mp 55.5–56 °C.

^{1}H NMR ($CDCl_3$): δ = 1.13/1.16 (2t, J = 7.2 Hz, 3H, CH_2CH_3), 1.34/1.37/1.43/1.50 (4s, 9H, Boc-Me), 3.10/3.11/3.15/3.17 (4s, 3H, N-Me), 3.36–3.66 (complex, 2H, N-CH_2), 5.18, 5.10/5.26, 5.08 (2ABq, J = 12.4 Hz, 2H, Z-CH_2), 7.31-7.37 (complex, 5H, Ph-H).

^{13}C NMR ($CDCl_3$): δ = 12.76/12.84/13.32/13.47 (CH_2CH_3), 28.13/28.31 (Boc-Me), 37.38/38.34/37.12/38.03 (N-Me), 42.88/42.81/44.69/44.59 (N-CH_2), 67.68/67.79/67.43 (Z-CH_2), 80.88/80.73/81.17/81.26 (Boc-C_q), 127.66, 127.89, 128.02, 128.06, 128.11, 128.29, 128.46, 136.02, 136.19, 136.26, 136.33 (Ar), 154.24/154.81/154.01/154.40 (Boc-CO), 156.57/156.11/156.83/156.27 (Z-CO).

Anal. Calcd for $C_{16}H_{24}N_2O_4$ (308.4): C, 62.32; H, 7.84; N, 9.08. Found: C, 62.4; H, 7.9; N, 9.2.

1-(Benzyloxycarbonyl)-2-ethyl-1-methylhydrazine (2):

Recrystallized **1** (2.10 g, 6.81 mmol) was dissolved in CH_2Cl_2/TFA (2:1, 35 mL) and left to react for 2 h while protected from atmospheric moisture. After evaporation to complete dryness the oily residue was partitioned between CH_2Cl_2 (60 mL) and 30% aq K_2CO_3 (30 mL) and the aqueous layer further extracted with CH_2Cl_2 (10 mL), whereupon the combined extracts were washed with brine (30 mL) and dried (Na_2SO_4). Removal of the solvent left a colorless liquid (1.41 g, 99%, after drying under high vacuum). This crude product was essentially pure by TLC (A, B) and suitable for further work.

^{1}H NMR ($CDCl_3$): δ = 1.07 (t, J = 7.2 Hz, 3H, CH_2CH_3), 2.89 (q, J = 7.2 Hz, 2H, N-CH_2), 3.10 (s, 3H, N-Me), 4.42 (br s, 1H, NH), 5.15 (s, 2H, Z-CH_2), 7.30–7.39 (complex, 5H, Ph-H).

^{13}C NMR ($CDCl_3$): δ = 12.84 (CH_2CH_3), 37.04 (N-Me), 44.15 (N-CH_2), 67.43 (Z-CH_2), 127.91, 128.08, 128.50, 136.50 (Ar), 156.76 (CO).

1-(Benzyloxycarbonyl)-2-ethyl-2-(4-fluorobenzoyl)-1-methylhydrazine (3):

Crude **2** (1.39 g, 6.68 mmol) was dissolved in anhyd pyridine (20 mL), and the clear solution cooled in ice under argon. 4-Fluorobenzoyl chloride (1.32 g, 8.32 mmol) was then introduced dropwise with rapid stirring over 15 min, whereafter stirring was continued overnight at r.t. Most of the pyridine was then stripped off at reduced pressure and the semisolid residue was partitioned between Et_2O (150 mL) and 0.2 M citric acid (75 mL), the colorless Et_2O extract was washed in turn with 0.2 M citric acid, 1 M $NaHCO_3$ and brine (3×40 mL each) and dried ($MgSO_4$). Removal of the solvent left a pale yellow oil weighing 2.22 g (100%) after thorough drying. TLC (A, B) gave essentially one spot. It could be purified by column chromatography (B; recovery 93%) and subsequently obtained as white crystals from light petroleum (100 mL/g) after several days at –20 °C; mp 40–40.5 °C.

^{1}H NMR ($CDCl_3$): δ = 1.22/1.27 (2t, J = 7.1 Hz, together 3H, CH_2CH_3), 3.07 (perturbed br signal, 3H, N-Me), 3.71 (unresolved br signal, 2H, N-CH_2), 4.97–5.10 and 5.16–5.23 (complex, 2H, Z-CH_2), 6.93 (br signal) and 7.20–7.43 (complex, 9H, Ar-H).
^{13}C NMR ($CDCl_3$): δ = 12.67/13.25 (CH_2CH_3), 37.60/38.38/38.07 (N-Me), 42.50/42.86/45.99 (N-CH_2), 68.28/67.98 (Z-CH_2), 115.28 (d, $^2J_{C,F}$ = 20.8 Hz, $C_{3,5}$), 127.87, 128.28, 128.51, 128.59, 131.25, 131.54, 135.42, 135.84 (Ar), 155.47 (Z-CO), 163.50 (d, $^1J_{C,F}$ = 250.3 Hz, C_4), 171.32/171.82 (4-FC_6H_4CO).
Anal. Calcd for $C_{18}H_{19}FN_2O_3$ (330.4): C, 65.44; H, 5.80; N, 8.48. Found: C, 65.4; H, 5.8; N, 8.6.

1-Ethyl-1-(4-fluorobenzoyl)-2-methyl-2-(tosylcarbamoyl)hydrazine (5):
Recrystallized **3** (330 mg, 1.00 mmol) was dissolved in MeOH (6 mL) and hydrogenolyzed for 2 h at atmospheric pressure over 5% Pd/C (60 mg). The catalyst was filtered off and the product was worked up essentially as described for **2**. The crude, chromatographically pure 1-ethyl-1-(4-fluorobenzoyl)-2-methylhydrazine **(4)** was obtained as a colorless liquid (191 mg, 97%). This product was dissolved in anhyd CH_2Cl_2 (1 mL) and cooled in ice under argon, whereupon a solution of tosyl isocyanate (193 mg, 0.98 mmol) in anhyd CH_2Cl_2 (1 mL) was introduced dropwise with rapid stirring over 10 min and left for a few hours under stirring in ice. A white precipitate was formed, from which the solvent was stripped off. The solid residue was triturated with cold Et_2O and chilled overnight, the insoluble product was collected by filtration, repeatedly rinsed with cold Et_2O and dried in vacuo to give crude, chromatographically pure **5** (C; 382 mg, 97% from **3**); microcrystalline solid; mp 217–219 °C (dec) ($CHCl_3$; –20 °C; 20 mL/g).
^{1}H NMR (DMSO-d_6): δ = 1.14 (perturbed t, J = 7.1 Hz, 3H, CH_2CH_3), 2.42/2.37 (2s, 3H, Ts-Me), 2.72, 3.10 and 3.60 (br signal, together 5H, N-Me + N-CH_2), 6.96–7.69 (br signal) and 7.43/7.36 (2d, J = 7.7/8.3 Hz) and 7.78/7.71 (2d, J = 8.2/8.3 Hz, together ~8H, Ar-H), 11.82/11.42 (br signal, 1H, NH).
^{13}C NMR (DMSO-d_6): δ = 11.61/12.30 (CH_2CH_3), 21.03/20.87 (Ts-Me), 36.1, 41.6, 42.2, 45.4 (br signal, partly obscured by solvent, N-Me + N-CH_2), 114.90 (d, $^2J_{C,F}$ = 21.2 Hz, $C_{3,5}$), 125.59, 127.52, 128.20, 128.83, 129.32, 130.0, 131.79, 136.98, 141.42, 141.81, 143.74 (Ar), 151.82 (br urea-CO), 162.62 (d, $^1J_{C,F}$ = 246.3 Hz, C_4), 170.73 (br, 4-FC_6H_4CO).
Anal. Calcd for $C_{18}H_{20}FN_3O_4S$ (393.44): C, 54.95; H, 5.12; N, 10.68. Found: C, 54.6; H, 5.2; N, 10.6.

1-Ethyl-1-(4-fluorobenzoyl)-2-methyl-2-[(4-phenylbutyl)tosylcarbamoyl]hydrazine (6):
Recrystallized **5** (492 mg, 1.25 mmol) was suspended in anhyd THF (5 mL; freshly distilled from Na/Ph_2CO) and 4-phenylbutanol (235 mg, 1.56 mmol) added with gentle mixing under argon. Anhyd Ph_3P (492 mg, 1.56 mmol) was introduced in one portion and after a few minutes the resulting turbid mixture was treated with diethyl azodicarboxylate (340 µL, 2.19 mmol) dropwise with rapid stirring over 15 min until a pale yellow color prevailed. The now clear mixture was then stirred for 15 h with exclusion of moisture. The solvent was stripped off at reduced pressure and the yellow oily residue was dissolved in CH_2Cl_2 and again taken to complete dryness. The residual semisolid material was dissolved in CH_2Cl_2 and applied to a silica gel column packed in CH_2Cl_2/Et_2O 20:1. Slow elution gave first a yellowish forerun (discarded) and then the desired compound as a pure (C) colorless glassy oil (403 mg, 61%), which failed to crystallize after prolonged standing at –20 °C.
^{1}H NMR ($CDCl_3$): δ = 1.22 (br signal, 3H, CH_2CH_3), 1.63 [br signal, 4H, $PhCH_2(CH_2)_2$], 2.38 (s, 3H, Ts-Me), 2.57 (br signal, 2H, $PhCH_2$), 3.36, 3.49 and 3.78 (br signal, together 5H, N-Me + N-CH_2CH_3), 4.22 [br signal, 2H, $Ph(CH_2)_3CH_2$], 7.04–7.29 (complex), 7.44 and 7.80 (br signal, together 13H, Ar).
^{13}C NMR ($CDCl_3$): δ = 12.95/13.41 (CH_2CH_3), 21.38 (Ts-Me), 27.34 ($PhCH_2CH_2$), 28.21 ($Ph(CH_2)_2CH_2$), 35.17 ($PhCH_2$), 39.63/41.69 (N-Me), 47.57/43.67 (CH_3CH_2), 71.37/70.89 [$Ph(CH_2)_3CH_2$], 115.42 (d, $^2J_{C,F}$~17 Hz, $C_{3,5}$), 125.80, 125.90, 128.28, 128.35, 129.07, 130.27 (Ar), 141.55/142.01 (Ts-C_1), 155.49 (br urea-CO), 163.86 (d, $^1J_{C,F}$ = 250.9 Hz, C_4),170.52 (br, 4-FC_6H_4CO).

1-(Benzyloxycarbonyl)-2-ethyl-1-methyl-2-(tosylcarbamoyl)hydrazine (7):
Synthesized from **2** and tosyl isocyanate essentially as described for **5**. The yield of crude pure (C) product was 99% in a 5 mmol run; white, lustrous crystals with mp 117–119 °C (CH_2Cl_2/Et_2O 1:20; –20 °C; 60 mL/g).
^{1}H NMR ($CDCl_3$): δ = 1.06 (perturbed t, J = 7.3 Hz, 3H, CH_2CH_3), 2.40 (s, 3H, Ts-Me), 3.12 (s, 3H, N-Me), 3.39 and 3.52 (ABq, further split by coupling to Me, J_1 = 14.4 and J_2 = 7.2 Hz, 2H, CH_2CH_3), 5.04 and 5.09 (ABq, J = 11.9 Hz, 2H, Z-CH_2), 7.23–7.32 (complex, 7H, Ph-H + Ts-$H_{3,5}$), 7.86 (d, J = 8.2 Hz, 2H, Ts-$H_{2,6}$), 8.68 (br s, 1H, NH).
^{13}C NMR ($CDCl_3$): δ = 12.77 (CH_2CH_3), 21.62 (Ts-Me), 37.09 (N-Me), 42.07 (CH_2CH_3), 68.63 (Z-CH_2), 127.99, 128.18, 128.35, 128.55, 129.46, 135.10, 135.89 (Ar), 144.49 (Ts-C_1), 151.12 (urea CO), 155.67 (Z-CO).
Anal. Calcd for $C_{19}H_{23}N_3O_5S$ (405.48): C, 56.28; H, 5.72; N, 10.36. Found: C, 56.2; H, 5.8; N, 10.4.

1-(Benzyloxycarbonyl)-2-ethyl-1-methyl-2-[(trideuteromethyl)tosylcarbamoyl]hydrazine (8a):
Obtained by Mitsunobu alkylation of **7** with [$^2H_3$]MeOH as alkylating agent. Essentially by analogy with **6**, a 5 mmol run gave pure (A, B) **8a** as a colorless viscous oil in 79% yield which failed to crystallize even after prolonged storage at –20 °C.
^{1}H NMR ($CDCl_3$): δ = 1.23/1.27 (2t, J = 7.2 Hz, 3H, CH_2CH_3), 2.42 (s, 3H, Ts-Me), 3.25/3.31 (2s, 3H, N-Me), 3.64–3.81 (2 perturbed m, 2H, CH_2CH_3), 5.16 and 5.11/5.18 (ABq/s, J = 11.9 Hz, 2H, Z-CH_2), 7.29–7.36 (complex, 7H, Ph-H + Ts-$H_{3,5}$), 7.75/7.81 (2d, J = 8.3 Hz, 2H, Ts-$H_{2,6}$).
^{13}C NMR ($CDCl_3$): δ = 12.45 (CH_2CH_3), 21.57 (Ts-Me), 33.7–34.6 (2 overlapping m, $J_{C,D}$≈11 Hz, CD_3), 36.48/37.61 (N-Me), 45.73/45.10 (CH_2CH_3), 68.27/68.17 (Z-CH_2), 127.84, 128.24, 128.29, 128.31, 128.46, 128.56, 128.72, 128.75, 129.45, 133.44, 133.62, 135.52, 135.76 (Ar), 144.49/144.39 (Ts-C_1), 155.66, 155.75, 155.79, 156.31 (CO).

1-(Benzyloxycarbonyl)-2-ethyl-2-[(isobutyl)tosylcarbamoyl]-1-methylhydrazine (8b):
Synthesized from **7** and i-BuOH according to Mitsunobu. A 2.5 mmol run afforded pure (A, B) **8b** in 59% yield as a pale yellow oil.
^{1}H NMR ($CDCl_3$): δ = 0.84/0.91 [t/d, J = ~6/6.7 Hz, 6H, $CH(CH_3)_2$], 1.18/1.26 (2t, J = 7.2 Hz, 3H, CH_2CH_3), 1.83 and 1.94 (2 perturbed m, 1H, CH), 2.40/2.38 (2s, 3H, Ts-Me), 3.20/3.29 (2s, 3H, N-Me), 3.52–3.60 and 3.68–3.82 (complex, 2H, CH_2CH_3), 4.04/3.96/4.07/3.94/3.98 (5d, partly obscured, J = 6.3 Hz, 2H, i-Bu-CH_2), 5.15 and 5.12/5.22 and 5.12 (2ABq, J = 12.1 Hz, 2H, Z-CH_2), 7.21–7.40 (complex, 7H, Ph-H + Ts-$H_{3,5}$), 7.79/7.83 (2d, J = 8.2 Hz, 2H, Ts-$H_{2,6}$).
^{13}C NMR ($CDCl_3$): δ = 13.02/12.66 (CH_2CH_3), 18.84/18.97/18.82 [$CH(CH_3)_2$], 21.41/21.38 (Ts-Me), 27.92/27.85 ($CHMe_2$), 37.89/36.90 (N-Me), 46.17 and 46.37 (2N-CH_2), 68.31/68.45 (Z-CH_2), 125.76, 125.84, 128.17, 128.23, 128.43, 128.46, 128.91, 129.02, 135.74, 135.87 (Ar), 141.75/141.89/141.55/142.08 (Ts-C_1), 155.30, 155.51, 155.64, 155.83 (CO).

1-Ethyl-2-methyl-2-(tosylcarbamoyl)-1-[(trideuteromethyl)tosylcarbamoyl]hydrazine (10):
Chromatographed **8a** (380 mg, 0.90 mmol) was dissolved in MeOH (15 mL) and hydrogenolyzed for 2 h over 5% Pd/C. After filtration and evaporation, the residual colorless oil was dissolved in CH_2Cl_2

and again taken to dryness. This was repeated twice, whereafter the product was dried in high vacuo to give pure (A) **9** (251 mg, 97%). It was dissolved in CH_2Cl_2 (3 mL) and cooled in ice under argon. Tosyl isocyanate (172 mg, 0.87 mmol) in CH_2Cl_2 (1 mL) was introduced dropwise with rapid stirring over a few minutes, whereupon the reaction was allowed to proceed for 2 h at r.t. Traces of turbidity were filtered off and the filtrate taken to dryness, leaving a white crispy foam, which was triturated with cold light petroleum and left for 20 h at –20 °C. Filtration, rinsing with cold light petroleum and drying furnished chromatographically pure **10** (416 mg, 95% from **8a**); microcrystalline solid; mp 94–95 °C (softens from ~90 °C; EtOAc/light petroleum 1:3, 100 mL/g).
^{1}H NMR ($CDCl_3$): δ = 1.27 (t, J = 7.2 Hz, 3H, CH_2CH_3), 2.44 and 2.47 (2s, 3H each, Ts-Me), 3.12 (s, 3H, N-Me), 3.82, 3.90 (ABq, further split by coupling to Me, J_1 = 14.2 Hz, J_2 = 7.1 Hz, 2H, CH_2CH_3), 7.33 and 7.38 (2d, J = 8.1 Hz, 2H + 2H, Ts-$H_{3,5}$), 7.72 and 7.96 (2d, J = 8.3 Hz, 2H + 2H, Ts-$H_{2,6}$), 9.23 (br s, 1H, NH).
^{13}C NMR ($CDCl_3$): δ = 12.51 (CH_2CH_3), 21.63 and 21.66 (Ts-Me), 33.64 (m, $J_{C,D}$ = 22.4 Hz, CD_3), 33.68 (N-Me), 47.42 (CH_2CH_3), 128.32, 128.52, 129.42, 130.08, 131.67, 136.22 (Ar), 144.54 and 145.64 (Ts-C_1), 151.57 (Ts-NHCO), 156.48 [Ts-N(CD_3)CO].
Anal. Calcd for $C_{20}D_3H_{23}N_4O_6S_2$ (485.60): C, 49.47; H, 5.40; N, 11.54. Found: C, 50.0; H, 5.5; N, 11.0.

1-[(Benzyl)tosylcarbamoyl]-2-ethyl-1-methyl-2-[(trideuteromethyl)tosylcarbamoyl]hydrazine (11):
Recrystallized **10** (195 mg, 0.40 mmol) was suspended in THF (4 mL, freshly distilled from Na/Ph_2CO), benzyl alcohol (48 mg, 0.44 mmol) added and the mixture cooled in ice under argon. This was treated with Ph_3P (126 mg, 0.48 mmol) and after a few minutes dropwise over 15 min with diethyl azodicarboxylate (81 µL, 0.52 mmol), during which period the turbid mixture became clear, and then it was allowed gradually to reach r.t. The solvent was stripped off at reduced pressure and the remaining semisolid material chromatographed (silica gel, Et_2O/CH_2Cl_2 1:20). Slow elution afforded a pure (A, C) fraction which furnished a waxy solid (181 mg, 79%); white, microcrystalline solid; mp 115–116 °C (Et_2O/light petroleum 1:10, 20 mL).
^{1}H NMR ($CDCl_3$): δ = 1.29 (perturbed signal, 3H, CH_2CH_3), 2.39 and 2.43 (2s, 3H + 3H, Ts-Me), 3.37/3.49 (2 br s, 3H, N-Me), 3.84/3.72 (2 br signals, 2H, CH_2CH_3), 5.22 (s, 2H, Bn-CH_2), 7.24–7.36 (complex, 9H, Ph-H + 2 × Ts-$H_{3,5}$), 7.78 (perturbed signal, 4H, 2 × Ts-$H_{2,6}$).
^{13}C NMR ($CDCl_3$): δ = 12.53 (CH_2CH_3), 21.41 and 21.58 (Ts-Me), 34.21 (m, $J_{C,D}$ = 21.1 Hz, CD_3), 39.18/40.51 (N-Me), 46.40 (CH_2CH_3), 73.34 Bn-CH_2), 125.95, 128.60, 128.79, 129.10, 129.48, 133.69, 134.36, 141.38, 142.14, 144.51 (Ar), 155.40, 156.49 (CO).
Anal. Calcd for $C_{27}D_3H_{29}N_4O_6S_2$ (575.73): C, 56.33; H, 5.60; N, 9.73. Found: C, 56.3; H, 5.6; N, 9.5.

1-(*tert*-Butoxycarbonyl)-1-ethyl-2-methylhydrazine (12):
Recrystallized **1** (3.08 g, 10.0 mmol) was hydrogenolyzed in MeOH according to the procedure for **4**. A similar workup afforded a volatile colorless liquid with a sweetish aromatic odor. The yield of pure (A, B) **12**, suitable for further work, was 1.54 g (89%).
^{1}H NMR ($CDCl_3$): δ = 1.13 (t, 3H, CH_2CH_3), 1.48 (s, 9H, Boc-Me), 2.58 (s, 3H, N-Me), 3.36 (q, 2H, N-CH_2), 4.20 (br s, 1H, NH).
^{13}C NMR ($CDCl_3$): δ = 13.28 (CH_2CH_3), 28.40 (Boc-Me), 37.64 (N-Me), 43.60 (N-CH_2), 80.15 (Boc-C_q), 155.66 (CO).

1-(*tert*-Butoxycarbonyl)-1-ethyl-2-methyl-2-(tosylcarbamoyl)hydrazine (13):
Crude **12** (1.54 g, 8.86 mmol) was allowed to react with tosyl isocyanate (1.74 g, 8.83 mmol) according to the preparation of **5**. An analogous workup provided crude **13** as a white pure (C) solid (3.18 g, 97%). An analytical specimen was obtained by recrystallization from CH_2Cl_2/Et_2O ≈1:8 (≈90 mL/g) as white glittering crystals; mp 148–149 °C (dec).
^{1}H NMR ($CDCl_3$): δ = 1.16 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.38 (s, 9H, Boc-Me), 2.43 (s, 3H, Ts-Me), 2.92 (s, 3H, N-Me), 3.24 and 3.67 (2dq, J_1 ≈ 7 Hz, J_2 ≈ 14 Hz, 1H + 1H, N-CH_2), 7.33 (d, J = 8.1 Hz, 2H, Ts-$H_{3,5}$), 7.94 (d, J = 8.4 Hz, 2H, Ts-$H_{2,6}$), 8.27 (br s, 1H, NH).
^{13}C NMR ($CDCl_3$): δ = 12.39 (CH_2CH_3), 21.58 (Ts-Me), 27.93 (Boc-Me), 32.62 (N-Me), 42.41 (N-CH_2), 82.96 (Boc-C_q), 128.28 (Ts-$C_{3,5}$), 129.42 (Ts-$C_{2,6}$), 136.00 (Ts-C_4), 144.59 (Ts-C_1), 152.36 (urea CO), 154.09 (Boc-CO).
Anal. Calcd for $C_{16}H_{25}N_3O_5S$ (371.44): C, 51.74; H, 6.78; N, 11.31. Found: C, 51.7; H, 6.8; N, 11.3.

1-[(Benzyl)tosylcarbamoyl]-2-(*tert*-butoxycarbonyl)-2-ethyl-1-methylhydrazine (14):
Crude **13** (1.86 g, 5.00 mmol) was alkylated with benzyl alcohol by the Mitsunobu method outlined previously (see compound **11**). A similar chromatographic workup afforded the desired compound as a colorless viscous oil. The yield of crude, chromatographically pure **14** was 1.82 g (79%). Crystallization from light petroleum (25 mL/g) gave the analytical specimen as a white microcrystalline solid; mp 79.5–80 °C.
^{1}H NMR ($CDCl_3$): δ = 1.15 (br. signal, 3H, CH_2CH_3), 1.40/1.46 (2 br. signal, 9H, Boc-Me), 2.40 (s, 3H, Ts-Me), 3.37, 3.48 and 3.61 (3 br. signal, 5H, N-Me and CH_2CH_3), 5.15 (br. signal, 2H, Bn-CH_2), 7.24–7.31 (complex, 7H, Ph-H + Ts-$H_{3,5}$), 7.82 (d, J = 8.2 Hz, 2H, Ts-$H_{2,6}$).
^{13}C NMR ($CDCl_3$): δ = 12.68/13.38 (CH_2CH_3), 21.40 (Ts-Me), 28.13 (Boc-Me), 42.07/39.39 (N-Me), 43.05/46.21 (CH_2CH_3), 72.21/72.60 (Ph-CH_2), 81.74/82.01 (Boc-C_q), 125.92, 128.17, 128.34, 128.53, 129.07, 134.68, 134.74 (Ar), 141.75/141.94 (Ts-C_1), 153.48 (Boc-CO), 156.31 (urea-CO).
Anal. Calcd for $C_{23}H_{31}N_3O_5S$ (461.58): C, 59.85; H, 6.77; N, 9.10. Found: C, 59.8; H, 6.9; N, 9.1.

Attempted Preparation of 1-[(Benzyl)tosylcarbamoyl]-2-ethyl-1-methyl-2-(tosylcarbamoyl)hydrazine. Isolation of Debenzylated Analog 15:
Chromatographed **14** (1.028 g, 2.23 mmol) was dissolved in CH_2Cl_2 (15 mL), whereafter TFA (7.5 mL) was added dropwise under argon at r.t. The resulting clear solution was left for 2 h, whereupon the solvent was stripped off at reduced pressure. After thorough drying in high vacuo, the residue was dissolved in CH_2Cl_2 and again taken to dryness and subsequently dried in high vacuo. This procedure was repeated twice until the odor of TFA had almost disappeared. The remaining semisolid material was dissolved in CH_2Cl_2 (20 mL) and cooled in ice under argon. Et_3N (341 µL, 2.45 mmol) was cautiously added and after a few min tosyl isocyanate (483 mg, 2.45 mmol), dissolved in CH_2Cl_2 (3 mL), was introduced dropwise over 10 min. The reaction was allowed to proceed for 14 h at r.t., when evaporation left a white semisolid residue which was taken up in CH_2Cl_2 (100 mL). Extractive workup followed by removal of the solvent left a white solid residue which was thoroughly triturated with cold Et_2O and after brief cooling the fine-grained insoluble powder was collected by filtration, rinsed with cold Et_2O and dried in high vacuo. This gave 831 mg (80%) of pure **15**; microcrystalline white solid; mp 207–208 °C (dec.; $CHCl_3$; –20 °C; 10 mL/g).
^{1}H NMR ($CDCl_3$): δ = 1.01 (t, 3H, CH_2CH_3), 2.40 and 2.41 (2s, 3H each, Ts-Me), 2.98 (s, 3H, N-Me), 3.23 and 3.70 (2dq, J_1 = 14.2 Hz, J_2 = 7.1 Hz, 1H + 1H, CH_2CH_3), 7.29 and 7.30 (2d, J = 8.1 Hz, 2H + 2H, Ts-$H_{3,5}$), 7.89 and 7.91 (2d, J = 8.2 Hz, 2H + 2H, Ts-$H_{2,6}$), 8.62 and 8.86 (2 br s, 1H + 1H, NH).
^{13}C NMR ($CDCl_3$): δ = 11.75 (CH_2CH_3), 21.67 and 21.69 (Ts-Me), 33.77 (N-Me), 41.87 (CH_2CH_3), 128.32 and 128.42 (2 × Ts-$C_{3,5}$), 129.59 and 129.63 (2 × Ts-$C_{2,6}$), 135.54 and 135.57 (2 × Ts-C_4), 144.95 (2 × Ts-C_1), 152.16, 152.37 (2 × CO).
Anal. Calcd for $C_{19}H_{24}N_4O_6S_2$ (468.66): C, 48.69; H, 5.16; N, 11.95. Found: C, 48.6; H, 5.3; N, 12.0.

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