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# Synthesis of Substituted Hydrazines from Triprotected Precursors

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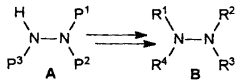
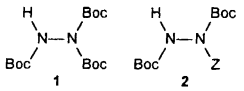
Full details related to the preparation and application of two triprotected reagents, 1,2,2-$Boc_3$-hydrazine (**1**) and 1,2-$Boc_2$-2-*Z*-hydrazine (**2**), for stepwise synthesis of substituted hydrazines are presented. In the presence of base these compounds undergo substitution at $N^1$, often accompanied by partial loss of protecting groups at $N^2$. Optimized alkylation procedures, eliminating or greatly diminishing these side reactions, involving phase-transfer catalysis are reported. The initial products can be selectively deprotected at $N^2$ to provide a new alkylation site. Twice alkylated derivatives of **1** and **2** differ in their potential to undergo further selective cleavage, and only the latter are capable of such. A limited number of partly protected substituted hydrazine derivatives have been made using the novel procedures. Compounds **1** and **2** both exist as mixtures of two conformers which have been assigned, whereas in alkylated derivatives up to four such are present. For two dialkylated compounds all conformers have also been assigned and their relative distribution experimentally determined. The results are in good agreement with those from theoretical calculations.

The synthesis of substituted hydrazines is not a straightforward business. Direct alkylation of hydrazine generally gives rise to mixtures of mono- to trisubstituted products, in which the substituents are attached to the same nitrogen atom, and is consequently not suitable for the preparation of hydrazine derivatives on a laboratory scale. In order to obtain high yields of intermediates and products and avoid lengthy purification procedures in such work, each step must obviously be carefully controlled. Although substituted hydrazines are key precursors of pyrazoles and related nitrogen heterocycles[1] and also components of pharmaceuticals, agrochemicals and dyestuffs, relatively little work dealing with methods for the controlled substitution of hydrazine has been reported[2–4] and a rational procedure for stepwise derivatization has long been missing. To eliminate this shortcoming, we recently introduced a couple of triprotected reagents **A** ($P^1$–$P^3$ are monovalent protecting groups),[5] that would fill this gap and in principle allow synthesis of tetrasubstituted derivatives of type **B** as well as partly substituted intermediates. The detailed description of the preparation, properties and use of two such reagents, **1**[6] (Boc = *tert*-butoxycarbonyl) and **2** (*Z* = benzyloxycarbonyl),[7] is the topic of this paper. Two additional reagents containing an aromatic sulfonyl group at $N^2$ have also been introduced, but their chemistry is not going to be treated in this context.





Reagents **1** and **2** both exhibit protection of one nitrogen atom as imidodicarbonates. Our syntheses of them both start from *Z*-hydrazine and are based on the fact that in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP) a Boc-group can be introduced into carbamates with $Boc_2O$, whereas in the absence of this catalyst only monosubstitution of amines takes place and carbamates do not react. These reactions are summarized in Scheme 1 (Troc = 2,2,2-trichlorethoxycarbonyl).

In the presence of base, compounds **1** and **2** undergo alkylation on their carbamate nitrogens. On the other hand, the imidodicarbonate functions involving the

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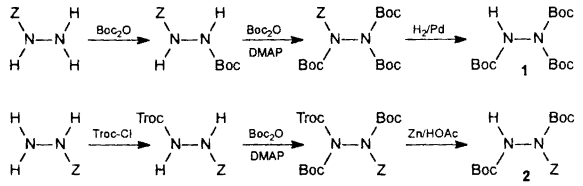
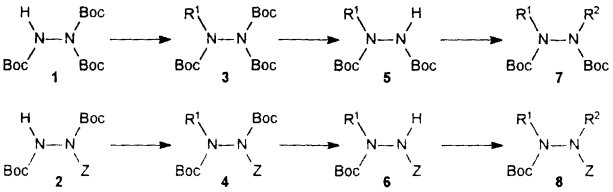


*Scheme 1.*

second nitrogen atom are sensitive to bases and nucleophiles and might therefore occasionally interfere in this step. One way to curb cleavage of these functions might be to perform the alkylations in two-phase systems in the presence of a phase-transfer catalyst. Therefore initially a systematic study on the alkylation of **1** in the presence of various bases was carried out. The experiences gained from this work were then applied to the alkylation of the related compound **2** (Scheme 2).



**R¹**=2,4-$(NO_2)_2C_6H_3$ (**3a**, **5a**); 2,4-$(NO_2)_2$-5-$FC_6H_2$ (**3b**, **5b**); Bn (**3c**, **4a**, **5c**, **6a**, **7c**, **7d**, **8a**); $CH_2CH_2CN$ (**3d**, **4b**, **5d**); Me (**3e**, **4c**, **6c**, **8c**); *n*-$C_6H_{13}$ (**3f**); 4-$NO_2C_6H_4CH_2$ (**3g**, **4d**, **5g**, **7g**); dansyl (**3h**); $C_3H_5$ (**4e**, **6e**, **8e**); $EtOCOCH_2$ (**4f**, **6f**, **8f**); **R²**=Me (**7c**, **8a**); $CH_2CH_2CN$ (**7d**); 2,4-$(NO_2)_2C_6H_2$ (**7g**); $EtOCOCH_2$ (**8e**); Bn (**8c**, **8f**).

*Scheme 2.*

Boc groups are generally cleaved by mild acidolysis. Compounds **3** and **4** contain three and two such groups, respectively, and these are obviously all not equivalent. Electron withdrawal caused by a second Boc or other alkoxycarbonyl group on the same nitrogen as well as that of the neighboring nitrogen obviously modulates their stability to acidic cleavage. The fine-tuning of the cleavage of just one Boc group from **3** and **4** is obviously the key to the successful application of **1** and **2** to the stepwise synthesis of substituted hydrazines.

To illustrate the synthetic potential of **1** and **2** in this context, a modest number of mono- and disubstituted hydrazines have been prepared and characterized, and they are listed below in Table 1. As is evident from their NMR spectra, all of them exist as mixtures of conformers. Two compounds, **7c** and **8c**, have been selected and studied in more detail from this point of view, and the data are collected below in Table 2.

## Results and discussion

Compound **1** was made by analogy with the corresponding ammonia derivative, $HNBoc_2$.[8] Like the latter it is a stable, crystalline solid and therefore easy to handle. $HNBoc_2$ undergoes alkylation and subsequent monodeprotection. Compounds **1** and **2** exhibit similar structural features, but **2** has an additional potential for selective deprotection.

Although a few derivatives of **1** have been described,[6] premature cleavage of protecting groups was occasionally noticed with competing dialkylation. To optimize the ratio between the rates of alkylation and premature cleavage of protective groups, an investigation of the effect of various bases was undertaken. As catalyst we invariably used tetrabutylammonium hydrogensulfate (TBAHS). Zwierzak *et al.*[9] applied a mixture of solid NaOH and $K_2CO_3$ in benzene to effect deprotonation of amides, and this procedure was shown to be very efficient also in conjunction with **1** (Procedure A), allowing a very short reaction to be used as a result of which essentially no premature loss of Boc was taking place. Without NaOH, using MeCN as solvent, reaction times were prolonged to hours instead of minutes, although conducted at 50 °C as employed previously by Landini and Penzo (Procedure B).[10]

In addition to the two solid–liquid systems described in the previous paragraph, we also investigated a liquid–liquid one (50% NaOH/benzene, Procedure C), used by Brehme to effect alkylation of anilides.[11] Benzylation of **1** was very fast, and the reaction was over within 5 min. Only an insignificant amount of dibenzylation could be detected as a result of premature deprotection. Benzylation of **1** was also effected in excellent yield by $KF/Al_2O_3$ in MeCN,[12] but the reaction required hours to go to completion. The same catalyst and solvent was also used for cyanoethylation of **1** with acrylonitrile,[13] but in this case the reaction was much faster and was over within a few minutes.

Whereas alkylation of **1** could be accomplished under a variety of experimental conditions, this was not the case for **2**, the reason being the high sensitivity of the benzyl *tert*-butyl imidodicarbonate function to base, leading to loss of the *Z*-function, a fact which has even been exploited preparatively for aminolysis.[14] Of the various experimental conditions discussed above and described in the experimental part, procedure C proved to be the most suitable, provided only 10–20% NaOH was used. With this precaution, **4a** was obtained as an oil in 98% yield. The cyanoethylated derivative **4b** was made in the presence of the milder catalyst KF/Celite[15] instead of $KF/Al_2O_3$ which gave rise to considerable cleavage in this case.

Whereas all bis-*tert*-butylimidodicarbonate derivatives of amines including amino acids we have attempted[4] could be selectively cleaved by mild acidolysis,[16] this was again not the case for such derived from **3** (procedure E), in which case further deprotection took place before the imidodicarbonate had been completely consumed as illustrated below. Fortunately $Mg(ClO_4)_2$ in MeCN[17] (procedure F) was found to effect perfectly regioselective cleavage of one Boc group from the imidodicarbonate function to give **5**, thus creating a new site for further alkylation at $N^2$. Compounds derived from **4** behaved similarly.

Using the methods discussed above, for all of which typical examples (procedures A–F) are given in the

*Table 1.* Selected substituted hydrazine intermediates prepared from **1** and **2**.

| Pprecursor/ product[b] | RX/procedure[a]/ m.p. (°C)/yield (%) | $^1$H NMR [$CDCl_3$, δ (ppm) rel. TMS, 270/400/500 MHz] |
|---|---|---|
| **1/3e** | MeI/A/oil/97 | 1.44/1.49 (9 H), 1.514/1.506 (18 H), 3.06/3.08 (3 H). |
| **1/3f** | *n*-$C_6H_{13}Br$/A/oil/94 | 0.88 (T, $J$=7 Hz, 3 H), 1.29 (m, 6 H), 1.51/1.44/1.50/1.49 (29 H), 3.40/3.37/3.43/3.35 (2 H). |
| **1/3g** | 4-$NO_2C_6H_4CH_2Br$/A/68–70/98 | 1.42/1.47/1.45/1.43 (27 H), 4.66/4.64 (2 H), 7.58 (d, $J$=9 Hz, 2 H), 8.18 (d, $J$=9 Hz, 2 H). |
| **1/3h** | dansyl-Cl/A/144.5-145.5/61 | 1.31 (18 H), 1.46 (9 H), 2.87 (6 H), 7.19 (d, $J$=7.5 Hz, 1 H), 7.49–7.60 (2 H), 8.43, 8.53, 8.63 (3 d, $J$=8.4, 7.4, 8.8 Hz, 3 H). |
| **2/4c** | MeI/C(10% NaOH)/57.5–59/88 | 1.34/1.47 (9 H), 1.51/1.49 (9 H), 3.08/3.09 (3 H), 5.19/5.20/5.22/5.23/5.28/5.30/5.33 (2 H), 7.27–7.40 (m, 5 H). |
| **2/4d** | 4-$NO_2C_6H_4CH_2Cl$/C (20% NaOH)/oil/93 | 1.380/1.416, 1.423/1.449 (18 H), 4.52, 4.56, 4.57, 4.61, 4.68, 4.69, 4.71, 4.73 (2 H), 5.06, 5.09, 5.12, 5.16, 5.23 (2 H), 7.28–8.06 (m, 9 H). |
| **2/4e** | $C_3H_5Br$/C(20% NaOH)/oil/99 | 1.34/1.47 (9 H), 1.50/1.48 (9 H), 4.00–4.13 (m, 2 H), 5.05–5.31 (m, 4 H), 5.77–5.87 (m, 1 H), 7.31–7.40 (5 H). |
| **2/4f** | $EtOCOCH_2Br$/C (10% NaOH)/oil/95 | 1.23/1.21 (t, $J$=7.2 Hz, 3 H), 1.33/1.46 (9 H), 1.51/1.49 (9 H), 4.08, 4.13, 4.26, 4.30 and 4.09–4.19 (4 H), 5.18–5.36 (8 sign., 2 H), 7.30–7.42 (m, 5 H). |
| **3a/5a** | —/E/134–135/95 | 1.52/1.42 (18 H), 7.01 (1 H), 7.88 (d, $J$=8.2 Hz, 1 H), 8.45 (dd, $J_1$ = 8.9 Hz, $J_2$ = 2.6 Hz, 1 H), 8.79 (d, $J$=2.6 Hz, 1 H) |
| **3b/5b** | —/E/134–135/93 | 1.52/1.47 (18 H), 6.99 (1 H), 7.61 (d, $J_{HF}$ = 8 Hz, 1 H), 8.73 (d, $J_{HF}$ = 7 Hz, 1 H) |
| **3c/5c** | —/E/102–103/89 | 1.48/1.44 (18 H), 4.64 (2 H), 6.24/5.98 (1 H), 7.26–7.35 (m, 5 H). |
| **3d/5d** | —/F/96.5–98/93 | 1.48/1.46 (18 H), 2.68 (2 H), 3.75 (t, $J$=7 Hz, 2 H), 6.54/6.32 (1 H). |
| **3g/5g** | —/E/108.5–110/74 | 1.45/1.48 (18 H), 4.73 (2 H), 6.34/6.48 (1 H), 7.49 (d, $J$=9 Hz, 2 H), 8.20 (d, $J$=9 Hz, 2 H). |
| **4c/6c** | —/F/oil/98 | 1.41 (9 H), 3.12 (3 H), 5.16 (2 H), 6.82/6.65 (1 H), 7.31–7.36 (m, 5 H). |
| **4e/6e** | —/F/oil/99 | 1.42 (9 H), 4.07 (2 H), 5.14, 5.16 (4 H), 5.82 (1 H), 6.42, 6.64 (1 H), 7.29–7.39 (m, 5 H). |
| **4f/6f** | —/F/oil/99 | 1.27 (t, $J$=7 Hz, 3 H), 1.46/1.40 (9 H), 4.19, 4.20, 4.27 (4 H), 5.17 (2 H), 6.95/6.68 (1 H), 7.28–7.35 (m, 5 H). |
| **5c/7c** | MeI/A/oil/96 | For detailed spectral data, see Table 2 |
| **5c/7d** | $CH_2CHCN$/CN/oil/93 | See Experimental under one-pot synthesis |
| **5g/7g** | 2,4-$(NO_2)_2C_6H_3Cl$/A/oil/91 | 1.53/1.40/1.59/1.60 (18 H), 4.62–5.28 (2 H), 7.16–7.7 (3 H), 8.01, 8.09 (d, $J\approx$8 Hz, 2 H), 8.38, 8.68 (d, $J\approx$8 Hz, 2 H). |
| **6a/8a** | MeI/C(50% NaOH)/oil/99 | 1.36/1.40/1.45/1.51 (9 H), 2.79/2.77/2.88/2.91 (3 H), 4.22/4.26/4.18/4.29 (2 H), 4.75–5.26 (20 sign., 2 H), 7.26–7.34 (m, 10 H). |
| **6c/8c** | BnBr/C(50% NaOH)/oil/97 | For detailed spectral data, see Table 2 |
| **6e/8e** | $EtOCOCH_2Br$/C (50% NaOH)/oil/95 | 1.25 (t, $J$=7.1 Hz, 3 H), 1.33/1.37/1.40/1.44 (9 H), 3.66–4.81 (4 H), 4.20 (q, $J$=7.1 Hz, 2 H), 5.06, 5.09, 5.12, 5.17, 5.22, 5.25 (4 H), 5.86–5.99 (1 H), 7.30–7.33 (m, 5 H). |
| **6f/8f** | BnBr/C(50% NaOH)/oil/95 | 1.16/1.38/1.23/1.46 (12 H), 3.44–4.77 (m, 6 H), 5.10–5.27 (2 H), 7.25–7.45 (m, 10 H). |

[a]For the procedures used, see Experimental. [b]For identification of the compounds made, see key in Scheme 2.

Experimental section, a number of compounds **3**–**8**, derived from **1** and **2**, were made as listed in Table 1. Inspection of Table 1 shows that most of these hydrazine intermediates exist as oils. In particular, this refers to all except one compound (**4c**) derived from **2**, whereas a few compounds **3** and especially **5** could be crystallized. This is essentially in agreement with previous experiences,[18] although intermediates derived from **A** above with $P^1/P^2/P^3$ = tosyl/Boc/Z in many cases gave rise to crystalline compounds.[19]

*Table 2.* Characteristic room temperature NMR chemical shifts and conformational equilibria in **7c** and **8c**.

| | Characteristic NMR chemical shifts of conformers | | | | | | Conformer distribution (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N–Me | | N–$BnCH_2$ | | Boc/Boc, Boc/Z | | | | | |
| | $^{13}C$ | $^{1}H$ | $^{13}C$ | $^{1}H$ | $^{13}C$ | $^{1}H$ | MM | AM1 | MM/2+ | Exp. |
| Conformer **7c** | | | | | | | | | | |
| *EE* | 36.22 | 2.78 | 51.99 | 4.34/4.71 | 80.64/80.91, 154.61/155.91 | | 88.3 | 45.6 | 66.9 | 66 |
| $Z_{Me}E$ | 38.39 | 2.71 | 52.47 | 4.17/5.04 | 80.81/80.84, 154.89/155.60 | | 8.7 | 27.4 | 18.1 | 18 |
| $E_{Me}Z$ | 36.14 | 2.97 | 54.04 | 4.32/4.67 | 80.52/81.35, 153.89/155.84 | | 2.5 | 17.7 | 10.1 | 11 |
| *ZZ* | 38.05 | 2.82 | 54.09 | 4.25/4.94 | 81.03/81.49, 154.40/155.09 | | 0.5 | 9.3 | 4.9 | 5 |
| Conformer **8c** | | | | | | | | | | |
| *EE* | 36.30 | 2.81 | 52.82 | 4.39/4.79 | 27.92, 81.00, 155.79, 67.81, 154.88 | 1.25 | 62.6 | 58.2 | 60.4 | 62 |
| $Z_{Me}E$ | 38.39 | 2.71 | 52.99 | 4.29/5.11 | 28.13, 81.27, 154.64, 67.81, 156.35 | 1.40 | 31.7 | 23.1 | 27.4 | 18.5 |
| $E_{Me}Z$ | 35.99 | 2.86 | 53.78 | 4.36/4.76 | 27.95, 80.88, 155.48, 67.92, 154.90 | 1.31 | 4.4 | 16.4 | 10.4 | 12 |
| *ZZ* | 37.97 | 2.81 | 53.84 | 4.36/5.03 | 28.23, 81.40, 155.11, 68.06, 155.39 | 1.48 | 1.3 | 6.8 | 4.0 | 7.5 |

The second striking feature of the compounds in this table is the complexity of their NMR spectra, as already noticed in our previous work,[6,7] indicating the presence of *E* and *Z* conformers. Thus, in the spectrum of **1**,[6] two signals for NH were observed, and by $^{13}C$ NMR spectroscopy we have now been able to characterize two conformers, present in the ratio 2:1 in several solvents (chloroform, pyridine, methanol and acetone). From a study, now in progress, we conclude that the *Z* configuration prevails in these solvents. It should also be mentioned that in 1,2-$Boc_2$-hydrazine three conformers (*ZZ*, *EZ* and *EE*) coexist, whereas $Boc_4$-hydrazine gave a simple spectrum without evidence of conformers,[20] a fact which has now also been verified at higher field. The low electron density on diacylated nitrogens obviously does not allow their free electron pairs to interact with the $sp^2$ carbons over the N–C bonds which is the basis of *Z,E* isomerism.

Assignment of the conformers is important from the point of view of conformational analysis. This is not a trivial task, because no characteristic H–H coupling constants are present in the N–C(O)O moieties. Even in the case of simple 1,2-diacylated dialkyl hydrazines the assignment of conformers has been left open.[21] Our systematic NMR studies of acylated hydrazine derivatives reveal that carbonyl $^{13}C$ chemical shifts are highly diagnostic for the assignment of observed conformers. These assignments can be further corroborated by theoretical calculations. Unambiguous assignments in acylated hydrazines is based on the difference in long-range five-bond H–H coupling constants across the CN bond (manuscript in preparation). In the case of alkoxycarbonylated hydrazines the largest differences are observed not on carbonyls but on $sp^3$ carbons connected to hydrazine nitrogens. This regularity in the chemical shifts of these carbons is similar in acylated and alkoxycarbonylated hydrazines and are the basis for the assignments below. As an illustration of this approach, the relevant data for two compounds (**7c** and **8c**) are given in Table 2. The results from conformational analysis by the MM (Merck) and AM1 (Spartan SGI 5.0.1) methods are also given in this table. Conformational analysis was performed by constraining the dihedral angles at the urethane bonds to 0 and 180°, calculating the mean conformational energy of individual conformers from the Boltzmann distribution, and on the basis of these the mean conformational energies of the conformer distribution of the compound was calculated. As the data in Table 2 show, the correct order of conformer distribution is predicted by both methods, MM calculations overestimating and AM1 calculations underestimating the differences in the conformational energies. By using the mean value from these calculations the experimental conformer distribution is excellently predicted (**7c**). Thus introduction of additional alkyl substituents at the nitrogen atoms of acylated or alkoxycarbonylated hydrazines shifts the equilibrium from *Z* towards *E* configuration in parallel with the preferences of the peptide bond.

Compounds of type **8** contain one Boc and one *Z* group which are orthogonal, and such hydrazine derivatives have previously been converted to tetrasubstituted hydrazines in which all substituent are different.[18,22] Therefore, in principle compound **2** is applicable for this purpose, whereas **1** is more convenient for the synthesis of 1,2-disubstituted hydrazines, since it is simpler to make and the two remaining Boc groups can be removed simultaneously.

## Experimental

All solvents used in the synthetic procedures were dried over molecular sieves (4A). TLC was performed on silica plates (Merck DC-Fertigplatten, Kieselgel 60 $F_{254}$). Melting points were determined on a Gallenkamp apparatus and are uncorrected. $^{1}H$ NMR spectra were recorded at 270, 400 and 500 MHz and $^{13}C$ NMR spectra at 67.8, 100 and 125.7 MHz on JEOL JNM EX270 and EX400 and Bruker AMX500 instruments (with $SiMe_4$ as internal

standard). The second instrument was also used to obtain $^{19}F$ NMR spectra at 376 MHz (with $CFCl_3$ as internal standard and referenced to $\delta_{CFCl_3}$ 0 ppm) and $^{15}N$ spectra at 40.4 MHz (with $HCO^{15}NH_2$ as external standard and $\delta_{HCO^{15}NH_2}$ 113.2 ppm). For conformers, shifts are given in order of decreasing intensity within slashes. Elemental analyses were made by Mikrokemi AB, Uppsala, Sweden.

*$Boc_3$-hydrazine* (**1**).[6] For experimental procedure and $^1H$ NMR spectrum, see Ref. 6. $^{13}C$ NMR (125.7 MHz, $CDCl_3$): δ (*Z* isomer) 27.74, 83.73, 150.88 ($Boc_2$), 27.99, 81.54, 153.99 (Boc); (*E* isomer) 27.74, 83.51, 150.44 ($Boc_2$), 27.93, 81.67, 154.05 (Boc); *Z*/*E* isomer ratio 2:1. $^{15}N$ NMR (40.4 MHz, $CDCl_3$): δ 109.98/110.62 (NH), 142.18 ($NBoc_2$). Found: C 54.3; H 8.6; N 8.4. Calc. for $C_{15}H_{28}N_2O_6$ (332.40): C 54.20; H 8.49; N 8.43.

*1,2-$Boc_2$-2-Z-hydrazine* (**2**).[7] A solution of Troc-Cl (6.48 g, 30 mmol) in $Et_2O$ (20 ml) was added to a vigorously stirred mixture of *Z*-hydrazine (4.98 g, 30 mmol) and $Et_3N$ (3.09 g, 30 mmol) in $Et_2O$ (100 ml) over a period of 1 h. After stirring for another hour, TLC (EtOAc/light petroleum 1:1) indicated that the reaction was over. Water was added to dissolve the precipitate and the ether layer separated, washed with water and 0.2 M citric acid and dried ($MgSO_4$). After evaporation the white solid was recrystallized from $Et_2O$/light petroleum to give 9.27 g (90%) of 1-Troc-2-*Z*-hydrazine with m.p. 132.5–134 °C. For spectral data, see Ref. 7. To a stirred mixture of this intermediate (12.0 g, 35.1 mmol) and $Boc_2O$ (19.2 g, 88 mmol) in MeCN (35 ml) solid DMAP (10 mg, 0.08 mmol) was added. After 5 min reaction with violent gas evolution, TLC (EtOAc/light petroleum 1:5) indicated that the reaction was complete, and most of the solvent was evaporated under reduced pressure. The residue was dissolved in $Et_2O$ and extracted with 0.2 M citric acid (five times), sat. NaCl, 1 M $NaHCO_3$ and sat. NaCl and dried ($MgSO_4$). Evaporation afforded a colourless oil (24 g), containing also $Boc_2O$, but suitable for direct use in the next step. A small amount of this oil was chromatographed on silica, but this sample also failed to crystallize. To the vigorously stirred solution of crude 1,2-$Boc_2$-1-Troc-2-*Z*-hydrazine (24 g, ca. 35 mmol) in acetic acid (150 ml) was carefully added Zn dust (24 g) with external water cooling. After 30 min the reaction was finished and remaining Zn was filtered off. The solution was diluted with water (1 l) and extracted with $Et_2O$ (three times), and the combined extracts were washed with sat. NaCl, 1 M $NaHCO_3$ (three times) and sat. NaCl and dried ($MgSO_4$). Evaporation afforded a colourless oil which could be crystallized from $Et_2O$/light petroleum to give pure **2** (11.8 g, 92% overall yield) as white crystals. $^1H$ NMR (500.1 MHz, $CDCl_3$): δ (*Z* isomer) 1.47 (1-Boc), 1.49 (2-Boc), 5.16/5.38 ($J$ = 12.2 Hz, $CH_2$), 6.79 (NH), 7.37 (*o*), 7.35 (*m*), 7.35 (*p*); (*E* isomer) 1.36 (1-Boc), 1.51 (2-Boc), 5.21/5.28 ($J$ = 12.2 Hz, $CH_2$), 6.70 (NH), 7.39 (*o*), 7.32 (*m*), 7.32 (*p*); $^{13}C$ NMR (125.7 MHz, $CDCl_3$): δ (*Z* isomer) 27.90, 81.82, 153.90 ($^2J_{CNH}$ = 5.4 Hz) (all 1-Boc), 27.58, 84.29, 150.22 (all 2-Boc), 68.87, 128.07 (*o*), 128.36 (*m*), 128.40 (*p*), 134.71 (s), 152.34); (*E* isomer) 27.62, 81.99, 153.93 ($^2J_{CNH}$ = 7.5 Hz) (all 1-Boc), 27.71, 84.08, 149.94 (all 2-Boc), 68.49, 128.28 (*o*), 128.28 (*m*), 128.37 (*p*), 134.85 (s), 151.91; *Z*/*E* isomer ratio 2.5:1; $^{15}N$ NMR (40.4 MHz, $CDCl_3$): δ 109.89/~110.1 (NH), 140.90 (NZBoc). For further details, see Ref. 7.

*Model alkylation experiments with* **1**

*Procedure A.*[9] *1-(2,4-Dinitrophenyl)-1,2,2-$Boc_3$-hydrazine* (**3a**). In a solution of **1** (332 mg, 1 mmol) in benzene (1 ml) a mixture of finely powdered NaOH (140 mg, 3.5 mmol), $K_2CO_3$ (280 mg, 2 mmol) and TBAHS (34 mg, 0.1 mmol) was suspended. After 5 min stirring, 2,4-dinitrochlorobenzene (243 mg, 1.2 mmol) in benzene (1 ml) was added and allowed to react for 15 min, when TLC indicated that the reaction was complete. (In a second experiment at 0 °C a 45 min reaction time was required.) After dilution with benzene (10 ml) the mixture was poured into water. The benzene layer was carefully washed with water several times and dried ($MgSO_4$). Evaporation at reduced pressure furnished a yellow solid quantitatively which was crystallized from benzene/light petroleum to afford pure **3a** (428 mg, 86%) with m.p. 143–144 °C. $^1H$ NMR (270 MHz, $CDCl_3$): δ 1.52/1.51/1.43 (3 sign., 27 H, Boc), 7.33/7.48 (2 d, $J$ = 9.1/8.8 Hz, 1 H, $H_6$), 8.42 (dd, $J_1$ = 9.1 and $J_2$ = 2.6 Hz, 1 H, $H_5$), 8.82/8.86 (2 pert. d, $J$ = 2.5 Hz, 1 H, $H_3$). $^{13}C$ NMR (67.8 MHz, $CDCl_3$): δ 27.87/27.93/27.59 (3 sign., Boc), 85.46/85.41/86.64 (3 sign., $C_q$, Boc), 121.4, 122.5, 127.5, 138.5, 142.0, 144.0 (Ar) 149.8 and 150.8 (CO, Boc). Found: C 50.5; H 6.1; N 11.1. Calc. for $C_{21}H_{30}N_4O_{10}$ (498.49): C 50.60; H 6.07; N 11.24.

*Procedure B:*[10] *1-(2,4-Dinitro-5-fluorophenyl)-1,2,2-$Boc_3$-hydrazine* (**3b**). A mixture of 1,5-difluoro-2,4-dinitrobenzene (123 mg, 0.6 mmol), $K_2CO_3$ (140 mg, 1 mmol), TBAHS (17 mg, 0.05 mmol) and **1** (166 mg, 0.5 mmol) in MeCN (1.5 ml) was prepared with cooling in ice-water and subsequently heated to 50 °C under stirring for 5 h with TLC monitoring. After partitioning between water and $Et_2O$, the aqueous layer was extracted twice with $Et_2O$, and the combined organic extracts were washed with brine until neutral and dried ($Na_2SO_4$). Evaporation gave a solid which was recrystallized (attempted chromatography on a silica column partly cleaved off one Boc group) from $Et_2O$/light petroleum to give light yellow crystals (214 mg, 83%) with m.p. 124.5–125.5 °C; pure by TLC. $^1H$ NMR (270 MHz, $CDCl_3$): δ 1.54/1.51/1.44 (3 sign., 27 H, Boc), 7.07/7.21 (2 d, $J_{H6F}$ = 11 Hz, 1 H, $H_6$), 8.78/8.82 (2 d, $J_{H3F}$ = 7 Hz, 1 H, $H_3$). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 27.85/27.55 (2 sign., Boc), 85.76/85.83/87.11 (3 sign., $C_q$, Boc), 111.47/112.54 (2 d, $J_{C6F}$ = 26 Hz, $C_6$), 124.69 ($C_3$), 132.60/132.77 (2 pert. sign., $C_2$), 137.95 ($C_1$), 140.35

(d, $J_{C4F}=10.7$ Hz)/141.59 (d, $J_{C4F}=10.4$ Hz, $C_4$), 149.70/149.89 (CO, $Boc_2$), 150.50/149.15 (CO, Boc), 157.44 (d, $J_{C5F}=272$ Hz)/157.58 (d, $J_{C5F}=274$ Hz, $C_5$). $^{19}F$ NMR (376 MHz, $CDCl_3$): δ −107.52/−106.52 (2 dd, $J_{FH6}=11$ Hz, $J_{FH3}=7$ Hz). Found: C 49.1; H 5.7; N 10.7. Calc. for $C_{21}H_{29}FN_4O_{10}$ (516.48): C 48.84; H 5.66; N 10.85.

*Procedure C.*[11] *1-Benzyl-1,2,2-Boc$_3$-hydrazine* (**3c**). To a stirred mixture of **1** (1.66 g, 5 mmol), TBAHS (170 mg, 0.5 mmol), NaOH (50% solution, 5 ml) and benzene (5 ml), benzyl bromide (900 mg, 5.26 mmol) was added. After 5 min the reaction was over and beside **3c** only a trace of 1,2-dibenzyl-1,2-$Boc_2$-hydrazine could be detected (TLC in EtOAc/light petroleum 1:5). Dilution with benzene and washing several times with water as described under Procedure A gave an oil (2.11 g, quantitatively) which was purified by chromatography on silica in EtOAc/light petroleum 1:5 to give pure **3c** in ca. 80% yield which crystallized after several months in the refrigerator: m.p. 58–59 °C (from light petroleum. $^1H$ NMR (270 MHz, $CDCl_3$): δ 1.36/1.38 (2 sign., 18 H, $Boc_2$), 1.47/1.51 (2 sign., 9 H, Boc), 4.58/4.55 (2 sign., 2 H, $CH_2$), 7.26–7.36 (compl. sign., 5 H, Ph). $^{13}C$ NMR (67.8 MHz, $CDCl_3$): δ 28.1/28.6/27.0/28.8 (Boc), 53.0 ($CH_2$), 83.07/81.19/81.65 ($C_q$, Boc), 128.2, 128.7, 130.6, 136.0 (Ar), 149.97/150.04 (CO, $Boc_2$), 153.82/153.41 (CO, Boc). Found: C 62.32; H 8.36; N 6.76. Calc. for $C_{22}H_{34}N_2O_6$ (422.52): C 62.54; H 8.11; N 6.63.

*Procedure D.*[12] Compound **3c** was also made by an alternative procedure. A suspension of **1** (166 mg, 0.5 mmol), KF/$Al_2O_3$ (362 mg, ~2.5 mmol) and benzyl bromide (94 mg, 0.55 mmol) in MeCN (2 ml) was stirred with monitoring by TLC for 3 h, when the reaction was complete. The product was isolated by extraction as above and chromatographed on silica to give a pure oil (199 mg, 94%), identical with that prepared above.

*Cyanoethylation of* **1**. *1-(2-Cyanoethyl)-1,2,2-Boc$_3$-hydrazine* (**3d**). A solution of **1** (166 mg, 0.5 mmol) in MeCN (0.5 mL) was mixed with KF/$Al_2O_3$ (7 mg, 0.05 mmol) and acrylonitrile (36 µL, 0.54 mmol) and stirred for 10 min, when the reaction was complete. After partitioning between 0.2 M citric acid and EtOAc, the aqueous phase was extracted with EtOAc three times and the combined extracts washed to neutral with brine and dried ($Na_2SO_4$). Evaporation afforded a pure solid **3d** (190 mg, 98%). M.p. 58–59 °C (from light petroleum). $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.443, 1.518, 1.524, 1.531 (4 sign., 27 H, Boc), 2.64, 2.66, 2.67, 2.68, 2.69, 2.71 (6 sign., 2 H, $CH_2CN$); 3.71, 3.72, 3.73, 3.74, 3.76 (5 sign. together 2 H, N–$CH_2$). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 16.54/16.99 ($CH_2CN$); 27.89, 27.99, 28.04 (Boc); 45.89/46.86 (N–$CH_2$), 82.14, 82.85, 84.16, 84.19 ($C_q$, Boc); 117.79 (CN); 150.19, 150.42, 152.63, 153.31 (CO). Found: C 56.1; H 8.2; N 11.1. Calc. for $C_{18}H_{31}N_3O_6$ (385.46): C 56.09; H 8.11; N 10.90.

*Typical alkylation procedure for* **2**. *1-Benzyl-1,2-Boc$_2$-2-Z-hydrazine* (**4a**). Reagent **2** is very labile to base,[7] and therefore mild conditions are required in the alkylation step. Procedure C with less NaOH gave the best results: A mixture of **2** (1.46 g, 4 mmol), 20% NaOH (3 ml), TBAHS (136 mg, 0.4 mmol) and benzyl bromide (700 mg, 4.1 mmol) in benzene (7.5 ml), monitored by TLC, was quenched after stirring for 60 min by pouring into water and the product subsequently extracted with $Et_2O$, washed with brine and dried to give a colourless pure oil (1.79 g, 98%) which was used as such in further experiments. $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.346/1.331/1.353/1.466 (4 sign., 18 H, 2 × Boc), 4.50/4.69/4.98/5.21/4.47/4.72/5.24/4.95/4.59/5.22/5.04/5.25/5.00/4.63 (14 sign., together 4 H, 2 × $CH_2$), 7.22–7.36 (m, 10 H, 2 × Ph). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 27.98/27.59/27.62/28.16 (Boc), 52.59/54.69 (N–$CH_2$Ph), 68.56/68.70 (O–$CH_2$Ph), 81.55/83.64/82.04/83.70 ($C_q$, Boc), 127.61, 127.76, 128.00, 128.15, 128.18, 128.35, 128.39, 128.41, 128.48, 129.27, 129.98, 135.07, 135.13, 135.23, 135.79 (Ph), 149.71, 149.98, 151.82, 152.16, 153.52, 153.76 (CO).

*Cyanoethylation of* **2**. *1-(2-Cyanoethyl)-1,2-Boc$_2$-2-Z-hydrazine* (**4b**). This experiment was performed essentially as described for **1** using KF/Celite instead of KF/$Al_2O_3$. From **2** (366 mg, 1 mmol) in MeCN (1 ml), KF/Celite (100 mg, ~0.9 mmol) and acrylonitrile (200 µL, 2.8 mmol) after 3 h, filtering, washing and evaporation was obtained an oil in quantitative yield. $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.33, 1.47, 1.50, 1.52 (4 sign., 18 H, Boc), 2.57–2.66 (compl. sign., 2 H, $CH_2CN$); 3.67–3.81 (compl. sign. 2 H, N–$CH_2$), 5.21–5.33 (compl. sign., 2 H, $CH_2Ph$), 7.34–7.40 (m, 5 H, Ph). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 16.54/16.97 ($CH_2CN$); 27.83/28.02 (Boc); 45.89/46.84 (N–$CH_2$), 69.17/69.30 ($CH_2Ph$), 82.48, 83.21, 84.77, 84.83 ($C_q$, Boc); 117.72/117.62 (CN); 128.28, 128.54, 128.62, 128.68, 134.75, 134.80 (Ph), 149.77, 149.93, 151.84, 152.08, 152.62, 153.11 (CO).

*Selective cleavage of one Boc group*

*Procedure E with TFA.*[16] *1-Benzyl-1-Boc-2-Z-hydrazine* (**6a**). To a stirred solution of **4a** (1.532 g, 3.36 mmol) in $CH_2Cl_2$ (13.5 ml) was added $CF_3COOH$ (0.766 g) in the same solvent (4 ml) and left at RT for 24 h when TLC indicated the presence of three components: title compound, starting material and 1-benzyl-2-*Z*-hydrazine. The reaction mixture was evaporated to dryness, the remaining material dissolved in $Et_2O$ (15 ml) and neutralized by washing with $NaHCO_3$ and brine and the solution dried ($Na_2SO_4$). After evaporation the oily product (1.17 g) was purified by column chromatography on silica with EtOAc/light petroleum 1:5 as eluent. From the eluate was obtained 893 mg (79%) of **6a** as an oil, 100 mg of *1-benzyl-2-Z-hydrazine* as white crystals with m.p. 82.5–83.5 °C (from $Et_2O$/light petroleum) and 82 mg of starting material. The oil crystallized after several months in the refrigerator; m.p. 56–57 °C (from light petroleum). $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.43

(s, 9 H, Boc), 4.65 (s, 2 H, N–Bn), 5.14 (s, 2 H, O–Bn), 6.50/6.21 (2 sign., 1 H, NH), 7.24–7.51 (m, 10 H, 2 × Ph). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 28.11 (Boc), 52.59/54.21 (N–$CH_2$Ph), 67.50 (O–$CH_2$Ph), 87.51 ($C_q$, Boc), 127.62, 128.16, 128.28, 128.48, 128.53, 128.78, 129.10, 135.70 (2 × Ph), 155.15, 155.64 (2 × CO). Found: C 67.97; H 6.78; N 7.81. Calc. for $C_{20}H_{24}N_2O_4$ (356.42): C 67.40; H 6.79; N 7.86.

The following data were recorded for the side product *1-benzyl-2-Z-hydrazine*: $^1$H NMR (400 MHz, $CDCl_3$): δ 3.64 (br. sign., 1 H, N*H*–Bn), 4.00 (s, 2 H, N–Bn), 5.13 (s, 2 H, O–Bn), 6.39 (br. s, 1 H, NHCO), 7.24–7.34 (m, 10 H, 2 × Ph). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 55.65 (N–Bn), 67.09 (O–Bn), 127.56, 128.14, 128.28, 128.48, 128.54, 128.93, 136.01 137.27 (2 × Ph), 157.15 (CO). Found: C 70.1; H 7.1; N 11.2. Calc. for $C_{15}H_{16}N_2O_2$ (256.31): C 70.29; H 6.29; N 10.93.

*Procedure F.*[17] *1-Benzyl-1-Boc-2-Z-hydrazine* (**6a**). This compound was later prepared by an alternative procedure: To a stirred solution of $Mg(ClO_4)_2$ flushed with $N_2$ at 50 °C was added **4a** (192 mg, 0.42 mmol). According to TLC all starting material was consumed within 10 min and the reaction was quenched by pouring into a mixture of 1 M $KHSO_4$ and brine 1:1. The product was exhaustively extracted with $Et_2O$, the extracts washed with brine and dried ($Na_2SO_4$). After evaporation pure, colourless **6a** (188 mg, 98%) was obtained as an oil, identical by TLC with the product obtained by Procedure E.

*Cyanoethylation of* **1**, *Boc cleavage and alkylation. One pot synthesis of 1-(2-cyanoethyl)-2-benzyl-1,2-Boc$_2$-hydrazine* (**7d**). To a stirred solution of **1** (332 mg, 1 mmol) and $KF/Al_2O_3$ (14 mg, 0.1 mmol) in MeCN (1 ml), acrylonitrile (70 µl, 1.05 mmol) was added. After 15 min, when the reaction was complete, the reaction flask was placed in an oil bath at 50 °C and $Mg(ClO_4)_2$ (67 mg, 0.3 mmol) was added, while it was flushed with nitrogen. The reaction was complete within 10 min and the mixture was taken to dryness at reduced pressure. The solid residue was dissolved in MeCN (2 ml), and phase-transfer catalyst mixture ($K_2CO_3$: 280 mg, 2 mmol, NaOH: 140 mg, 3.5 mmol and TBAHS: 34 mg, 0.1 mmol) was added, followed by benzyl bromide (180 mg, 1.05 mmol). After 10 min the final step was over and the mixture was partitioned between 0.2 M citric acid and EtOAc. The usual work-up gave an oil, containing only traces of side products, which were removed on a short silica column (EtOAc/light petroleum 1:5). 332 mg of pure colourless oily **7d** were obtained (overall yield including chromatography 89%). $^1$H NMR (400 MHz, $CDCl_3$): δ 1.38, 1.42, 1.49, 1.51, 1.53 (5 sign., 18 H, Boc); 1.91–2.54 (br. sign., 2 H, $CH_2CN$), 3.23–3.59 (br. sign. 2 H, N–$CH_2$); 4.09–5.13 (16 sign. together 2 H, $CH_2$Ph); 7.28–7.38 (m, 5 H, Ph). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 16.25/16.57/16.81 ($CH_2CN$), 28.01, 28.08, 28.15, 28.23 (Boc), 47.18/46.74/47.95/47.89 (N–$CH_2$), 52.79/54.60/52.95/54.43 ($CH_2$Ph), 81.97/81.74/81.15/82.50/82.58/82.31 ($C_q$, Boc), 117.88/118.28/117.80 (CN); 128.01, 128.13, 128.62, 128.72, 128.98, 129.21, 129.53, 129.69, 136.33, 136.47, 136.88, 137.07 (Ph), 153.49, 153.69, 154.25, 154.80, 154.96, 155.41, 155.93 (CO).

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