Stepwise synthesis of tetrasubstituted hydrazines

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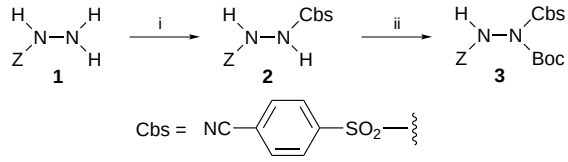
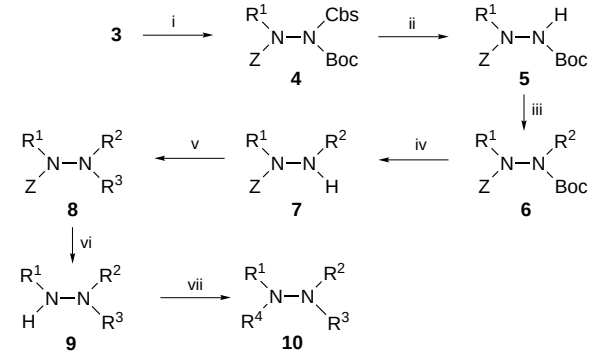
A new triprotected hydrazine reagent has been made and applied in alkylation/acylation reactions for stepwise synthesis of tetrasubstituted derivatives in high purity and yield.

In continuation of our efforts aiming at the simple synthesis of substituted hydrazines by a repetitive method,[1] we now present a first, easily made hydrazine derivative **3** with three *orthogonal* protecting groups. This reagent and products thereof allow alkylation and acylation and intermediate selective removal of protecting groups to take place under mild conditions and essentially quantitatively in all individual steps. Although, so far, our major efforts have been directed towards optimizing the overall reaction scheme with respect to the yield and purity of the intermediates **5**–**8** and products **10**, it is evident that this procedure affords simultaneously a high degree of molecular diversity.



Scheme 1 *Reagents and conditions*: i, CbsCl, pyridine, 94%; ii, Boc_2O, DMAP, MeCN, 93%

The starting material for the key reagent **3** is Z-substituted hydrazine **1**, liberated from the corresponding hydrochloride.[2] Using commercially available 4-cyanobenzenesulfonyl (Cbs) chloride,[3] this is easily converted to **2** with two amide functions of obviously different acidity (Scheme 1),[4] which therefore allows regioselective reaction with Boc_2O in the presence of DMAP at the sulfonamide nitrogen[5] to give the triprotected



Scheme 2 *Reagents and conditions*: i, R^1OH, PPh_3, DEAD, THF, 80–99%; ii, Al(Hg), CO_2, aq. Et_2O, 92–99%; iii, R^2X (X = Br or I), K_2CO_3–NaOH, Bu_4NHSO_4, C_6H_6, 92–100% or 2,4-$(O_2N)_2C_6H_3F$, K_2CO_3, Bu_4NHSO_4, MeCN, 85–97%; iv, TFA, CH_2Cl_2, 93–99%; v, R^3Cl, pyridine, 86–99%; vi, TFA (reflux); vii, $R^4{}_2O$ or 4-$FC_6H_4SO_2Cl$ (reflux), 72–98%

Table 1 Synthesis of hydrazines **4**–**10**

	R^1	R^2	R^3	R^4	Yield (%)	Mp/°C
4a	Bn	—	—	—	98	105–105.5
4b	4-$ClC_6H_4CH_2$	—	—	—	99	93.5–94
4c	4-$MeOC_6H_4CH_2$	—	—	—	97	111–111.5
4d	(*S*)-EtMeCHCH$_2$	—	—	—	80	oil
5a	Bn	—	—	—	92	65–65.5
5b	4-$ClC_6H_4CH_2$	—	—	—	99	89.5–90
5c	4-$MeOC_6H_4CH_2$	—	—	—	92	103.5–104
5d	(*S*)-EtMeCHCH$_2$	—	—	—	94	80.5–81
6aa	Bn	Me	—	—	100	oil
6ab	Bn	CH_2CO_2Et	—	—	97	oil
6ac	Bn	2,4-$(O_2N)_2C_6H_3$	—	—	95	129–130
6ba	4-$ClC_6H_4CH_2$	Me	—	—	99	oil
6bb	4-$ClC_6H_4CH_2$	2,4-$(O_2N)_2C_6H_3$	—	—	85	105–106
6ca	4-$MeOC_6H_4CH_2$	CH_2CO_2Et	—	—	93	oil
6cb	4-$MeOC_6H_4CH_2$	2,4-$(O_2N)_2C_6H_3$	—	—	97	121.5–122
6cc	4-$MeOC_6H_4CH_2$	Me	—	—	99	oil
6d	(*S*)-EtMeCHCH$_2$	4-$O_2NC_6H_4CH_2$	—	—	92	oil
7aa	Bn	Me	—	—	99	oil
7ab	Bn	CH_2CO_2Et	—	—	93	oil
7b	4-$ClC_6H_4CH_2$	Me	—	—	99	oil
7d	(*S*)-EtMeCHCH$_2$	4-$O_2NC_6H_4CH_2$	—	—	95	oil
8aa	Bn	Me	4-FC_6H_4CO	—	99	101.5–102.5
8ab	Bn	CH_2CO_2Et	Bu^{t}CO	—	94	oil
8b	4-$ClC_6H_4CH_2$	Me	Bz	—	99	68–68.5
8d	(*S*)-EtMeCHCH$_2$	4-$O_2NC_6H_4CH_2$	$C_{10}H_7CO$	—	86	foam
10a	Bn	Me	4-FC_6H_4CO	4-$FC_6H_4SO_2$	72[a]	113.5–114.5
10b	4-$ClC_6H_4CH_2$	Me	Bz	Ac	98[b]	97–97.5
10d	(*S*)-EtMeCHCH$_2$	4-$O_2NC_6H_4CH_2$	$C_{10}H_7CO$	$ClCH_2CO$	96[c]	79–80

[a] From **8a**. [b] From **8b**. [c] From **8d**.

derivative **3** with three different protecting groups. The overall yield of **3** from **1** is 87%.†

Compound **3** easily undergoes the Mitsunobu reaction with alcohols,[6] thereby giving rise to triprotected monosubstituted hydrazines **4** (Scheme 2). From compounds of this type the Cbs group can be cleaved reductively with Hg-activated aluminium to provide crystalline intermediates **5**, which are alkylated as previously described[1] under phase transfer conditions to give 1,2-diprotected 1,2-disubstituted hydrazine intermediates **6**. These differ from those described earlier in one important respect, namely, that their Boc and Z groups can be removed selectively in optional order. So far, we prefer to remove the Boc group first under mild acidic conditions *via* compounds **7** and subsequently acylate the latter to **8**. Finally, these can be deprotected under stronger acidic or catalytic hydrogenolysis conditions to give substances **9**, although we normally prefer to acylate them without isolation directly to the final products **10**.

A relatively large number of compounds **4**–**10** have been prepared to investigate and exemplify this scheme, all of which are listed in Table 1. No indication whatsoever of incomplete selectivity in the removal of the protecting groups in intermediates **4** and **6** has been detected. Alkylations and acylations of **5**, **7** and **9** were performed as described previously.[1] As can be seen from the table, all steps proceed very satisfactorily and few intermediates are obtained in less than 90% yield.

Mono- and di-alkylated hydrazines are extensively used as precursors in the synthesis of heterocycles.[7] Recently, Han and Janda also applied this methodology in their synthesis of α-aza amino acids.[8] Highly substituted hydrazines have found a number of practical applications.[9]

Although not demonstrated experimentally here, several other reactions of the amino group in addition to alkylation and acylation can be envisaged to be useful in this context, but we have confined ourselves to exemplify a few additional functional groups which can be introduced easily using the present conditions. Considering the large number of alkylating and acylating agents available, it seems reasonable to assume that the new reagent can be used for construction of chemical libraries. Further modification of functional groups present in compounds such as **10** could additionally increase the potential for molecular diversity inherent in these, at first glance, simple compounds.

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Footnotes

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† *Selected data* for **3**: ^{1}H NMR (400 MHz, $CDCl_3$, major conformer): δ 1.34 (s, 9 H, Boc), 5.18 and 5.24 (AB quartet, *J* 12.1 Hz, 2 H, CH_2), 7.14 (br s, 1 H, NH), 7.37 (perturbed signal, 5 H, Ph), 7.80 (d, *J* 8.3 Hz, 2 H, Cbs $H_{3,5}$), 8.24 (d, *J* 8.3 Hz, 2 H, Cbs $H_{2,6}$).

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