A selective method for cleavage of N-Troc-protected hydrazines and amines under mild conditions using mischmetal and TMSCl

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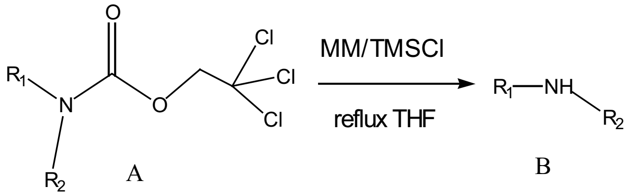
The Troc (2,2,2-trichloroethoxycarbonyl) protecting group was efficiently removed under neutral conditions from corresponding protected hydrazines and amines using mischmetal in good to excellent yields. Two new substituted hydrazines were synthesised.

Keywords: mischmetal, TMSCl, hydrazines, amines, deprotection

The Troc (2,2,2-trichloroethoxycarbonyl) group was introduced into organic synthesis by Woodward in 1966[1] in peptide chemistry. It is a stable protecting group which can be easily used for the masking of hydroxy and amino groups.[2] Therefore, this group has been an exceedingly useful protecting group in organic synthesis. It also allows selective protection of hydrazines in the presence of other protecting groups and it is possible to perform an orthogonal stepwise cleavage followed by substitution by another reagent.[3] This is a very useful feature that can be utilised in the preparation of protected hydrazines,[3] hydrazino acids and azapeptides.[4] The Troc group is generally removed by a reductive elimination process with Zn in 90% aqueous AcOH, which was also the original method for this purpose.[1] These classical deprotection conditions do not allow easily reducible or acid sensitive groups to be retained in substrates.[5] In addition, we have sometimes observed small amounts of by-products formed during the cleavage of the Troc group from Boc(Z)N–N(Troc)Boc {Z = benzyloxycarbonyl, Boc = *t*-butoxycarbonyl} with Zn in AcOH.[3] In order to prevent side reactions and to find better reaction conditions several modifications of the original method have been proposed – such as reduction using Zn–Cu in AcOH, Zn–Pb in AcOH, a Cd-Pb couple in AcOH and Cd in AcOH–DMF.[2] All these systems still need acidic condition in order to function as intended. Unlike the methods mentioned above, several new methods have been published in recent years wherein the Troc group has been cleaved under neutral conditions and in moderately polar systems such as Zn in MeOH, Zn–Cu or Zn–Ag couples in MeOH, Zn in THF–H_2O, Na–Hg alloy in THF–MeOH, Zn-*N*-methylimidazole in EtOAc or acetone[5] and in EtOH–H_2O.[6] Most of those new methods use zinc or its couples as the reducing reagent, but due to the variable quality of commercially available zinc powder, the reproduction of these procedures tends to be difficult. A method for removal of the Troc group by $(Bu_3Sn)_2$ in benzene or DMF under microwave radiation has also been published,[2] but this procedure was applied exclusively in the absence of other well known protecting groups such as Boc, Z, Fmoc and Ac.

Lately, numerous papers have been published where lanthanides and their salts were used in organic synthesis[7] including a method for cleavage of the Troc group.[8] Regardless of the good yields of some of the methods mentioned, many reagents employed are rather expensive (In, SmI_2) or possess considerable hazard for the environment (Cd, Pb, Hg). Thus, the aim of our work was to find a cheap, innocuous and easily reproducible method for removing the Troc group from corresponding protected amines and hydrazines under mild conditions. Herein we report the results of our studies by using mischmetal (50% Ce, 25% La, 16% Nd, 6% Pr)[9,10] for this purpose (see the Scheme). The main components of mischmetal have relatively high standard reduction potentials; hence mischmetal could be a sufficiently powerful alloy for the cleavage of the Troc group under neutral conditions. Moreover, the mischmetal is many times cheaper than the corresponding individual lanthanide.



R_1 = p-MeO-C_6H_4, Bn, Ph, Boc-NH, Ph-NH, Z-NH, Z(Boc)N

R_2 = H, Me, Boc, Ph

MM= mischmetal

Scheme 1

First, we tried to achieve the cleavage of Troc group under very simple reaction conditions. Thus, some simplest conditions were tested: mischmetal in MeOH with ultrasonic treatment, mischmetal in EtOH in the presence of catalytic amount of HCl and mischmetal in THF in the presence of 1 equivalent of H_2O. All these reactions were performed at room temperature as well as under reflux with a suitable solvent. Despite the known reaction of mischmetal with water and alcohols none of these attempts resulted in the cleavage of the Troc group. We also applied some of the reaction conditions reported in our previous work,[9] but no reaction occurred even on refluxing the reaction mixture for several hours. In order to facilitate the deprotection reaction different activators were studied: TMSCl, NH_4Cl and 1,2-dibromoethane. The most efficient cleavage of Troc group was observed when approximately 6 equivalents of mischmetal and 9 equivalents of TMSCl were used (Table 1, entry 12).

Having optimised the deprotection conditions, various Troc-protected hydrazines and aromatic and aliphatic amines were prepared, according to previously published methods[11] and subjected to the deprotection conditions described above (Table 1, entry 12). The results of removal of the Troc group from several hydrazines and amines under optimised reaction conditions are outlined in Table 2. It can be seen that the reaction proceeds smoothly to furnish the corresponding hydrazines or amines. In the course of these studies we confirmed that the activated mischmetal in THF is capable of removing the Troc protecting group in the presence of other common protecting groups such as Boc and Z. The cleavage of the Troc group was very selective except for compound entry 9 (Table 2) where the Boc group was also removed.

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Table 1 Optimisation of reaction conditions[a]

Entry	Compound	Metal[c]/equiv	Activators/equiv	Solvent	Conversion[e]/%
1	Z–NH–NH–Troc	3.9	TMSCl (3.8)	THF	<10
2	Ph–NH–NH–Troc	3.8	TMSCl, Br–CH_2–CH_2–Br (4: 1)	THF	50
3	Z–NH–NH–Troc	3.8	TMSCl, Br–CH_2–CH_2–Br (4: 1)	THF	50
4	Z–NH–NH–Troc	3.8	TMSCl, Br–CH_2–CH_2–Br (4: 1.6)	THF	>90
5	Ph–NH–Troc	3.8	TMSCl, Br–CH_2–CH_2–Br (4: 1,6)	THF	>90
6	*p*–CH_3O–Ph–NH–Troc	3.8	TMSCl, Br–CH_2–CH_2–Br (4: 1.6)	THF	50
7[b]	*p*–CH_3O–Ph–NH–Troc	2.0	NH_4Cl, (3)	EtOH: H_2O (3: 2)	<30
8	Ph–NH–NH–Troc	3.8	TMSCl, Br–CH_2–CH_2–Br (4: 1.6)	THF	>90
9	*p*–CH_3O–Ph–NH–Troc	3.8	Br–CH_2–CH_2–Br (1.6)	THF	0
10	*p*–CH_3O–Ph–NH–Troc	4.5	TMSCl, Br–CH_2–CH_2–Br (4: 2.3)	THF	>80
11	*p*–CH_3O–Ph–NH–Troc	6.1	TMSCl, Br–CH_2–CH_2–Br (4; : 1.6)	THF	>90
12	*p*–CH_3O–Ph–NH–Troc	6.1	TMSCl (9.3)	THF	>99
13	*p*–CH_3O–Ph–NH–Troc	6.1[d]	TMSCl (9.3)	THF	<10

[a] All the reactions performed under reflux.

[b] Reaction no. 7 was performed exactly under the conditions described in ref. 6 and was finished after 12 h.

[c] Mischmetal.

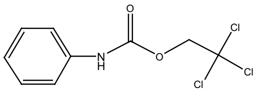
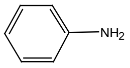
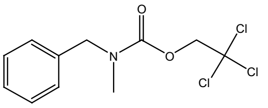
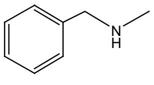
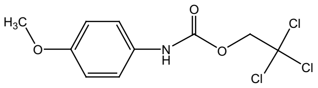
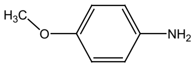
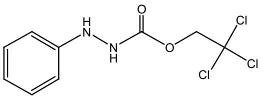
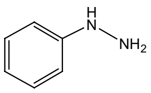
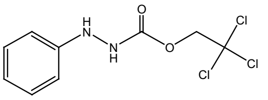
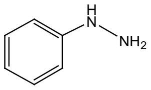
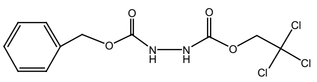
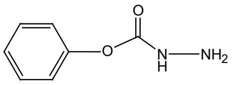
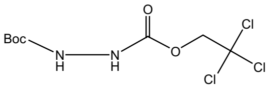
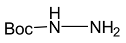
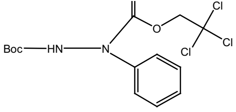
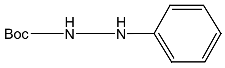
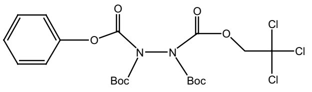
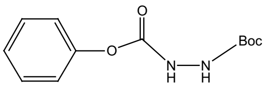
[d] In the reaction no. 13 only Zn was used and reaction was finished after 4 h.

[e] Extent of conversion was determined by TLC.

This result was expected because of the known destabilising influence of the Z group when both groups are at the same nitrogen. This phenomenon was demonstrated in our previous work[3] by the cleavage of the Boc group from the Boc(Z)N–N(CH_3)Boc in MeCN with $Mg(ClO_4)_2$ as a Lewis acid.

Thus, taking into account this phenomenon, it should be possible to cleave selectively one Boc group from bis-Boc-protected amines or hydrazines which include two Boc groups at the same nitrogen atom, but this research lies beyond our present goal. Other authors[12,13] have also reported that the Boc group undergoes reduction in stability if other protecting groups (Z, Boc, Ac) share the same nitrogen atom and consequently they could be easily cleaved with Lewis acids. Since during the activation of mischmetal the corresponding

Table 2 Deprotection of Troc group with mischmetal/TMSCl in THF

Entry	Starting material (A)	Product (B)	Time/h	Yield (isolated)/%
1			2	95
2			2	85
3			3	82
4			3	60
5*			3	83
6			3	>99
7		 $Boc{-}NH{-}NH_2$	2	>99
8			4	56
9			2,5	80

* For neutralisation of product B 5 Na_2CO_3 was used instead of $NaHCO_3$.

lanthanoid chlorides that act as Lewis acids were formed, this kind of deprotection reaction must take place. Indeed the behaviour of mischmetal under these conditions is interesting, as it allows selective cleavage of the Troc group from Troc(Boc)N in substituted hydrazines while the Boc group remains unchanged. This is a very good example of orthogonality by the cleavage of the Troc group. Taking into account that the Troc group is generally removed via a reductive elimination process, we propose that lanthanide chlorides formed during the activation of mischmetal act as mediators for deprotection of the Troc group. Low-valent lanthanoid salts also acts as reducing agents. For this purpose the mischmetal essentially acts as an electron donor. In the presence of water these salts can be hydrolysed effectively quenching the reaction. This could be the explanation for the reaction of cleavage having to be conducted in water-free environment.

Technically, the procedure was simple (see experimental section) and afforded generally good to excellent yields. In some cases better yields were obtained when a stronger base was used in the work-up. For example using saturated Na_2CO_3 solution instead of $NaHCO_3$ for the neutralisation process afforded remarkably better results (see Table 2, entries 4 and 5).

In summary, we have described a new mild and cheap deprotection method for the cleavage of the Troc group by using a mischmetal/TMSCl system in dry THF. The reactions in these conditions are relatively rapid and as a rule provide high yields. We have also demonstrated that this deprotection method could be successfully employed in the presence of Z and Boc groups. Thus, a simple, mild, cheap and reproducible protocol is reported.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200P spectrometer at 200 MHz and at 50 MHz respectively in $CDCl_3$ solution using TMS as reference. HRMS spectra were recorded on an Ettan ESI-ToF electrospray TOF MS instrument (Amersham Biosciences, Uppsala Sweden). GLC analyses were made on an HP 5890A instrument (FID detector), using fused silica capillary column 25 m × 0.25 mm (ID) with DB-5 liquid phase (0.25 μm).

Two novel starting compounds **7A** and **8A** were identified by NMR spectroscopic data and HRMS and/or elemental analysis.

7A: ^{1}H NMR ($CDCl_3$): δ = 1.48 (s, 9H Me Boc), 4.78 (s, 2 H, Troc), 6.6 (s, 1H, NH, Boc), 7.1 (s, 1H, NH, Troc). ^{13}C NMR ($CDCl_3$): δ = 28.2 (Me, Boc), 75.1 (CH_2, Troc), 82.2 ($C_{q,}$ Boc), 94.9 ($CCl_{3,}$), 155.1 and 155.4 (C=O). Compound was obtained as light yellow oil. HRMS *m/z* calc. for Na-adduct = 328.9839, found = 328.9856.

8A: ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 9H, Me, Boc), 4.86 (s, 2H, Troc), 6.60 (s, 1H, NH, Boc), 6.8–6.9/7.1–7.2 (m, 5H Ar). ^{13}C NMR ($CDCl_3$): δ = 28.3 (Me, Boc), 76.3 (CH_2, Troc), 85.3 ($C_{q,}$ Boc), 93.9 ($CCl_{3,}$), 113.0, 120.8, 129.2, 148.4 (Ar), 152.9 (C=O, Boc), 156.3 (C=O, Troc). M.p. = 59.5–60.0°C. $C_{14}H_{17}Cl_3N_2O_4$ calc. C 43.8 H 4.5 N 7.3. M 383.66 found C 43.8 H 4.4 N 7.3. HRMS *m/z* calc. for Cl-adduct = 416.9942, found = 416.9962. (^{35}Cl).

General procedure

The freshly filed mischmetal powder (grain size 0.1–0.3 mm) (380 mg, 2.7 mmol) was added to dry THF (10 ml) and activated with TMSCl (516 μl, 4.1 mmol) by refluxing for 20-30 min under an argon atmosphere. Then the Troc-protected hydrazine or amine (0.44 mmol) was added and the mixture was refluxed for the indicated time (Table 2). The progress of the deprotection reaction was monitored by TLC (EtOAc: Hex, usually 2 : 1) and before running the TLC the sample was neutralised with a saturated aqueous solution of $NaHCO_3$. When the reaction was complete the mischmetal powder was filtered off and the resulting filtrate was neutralised with a saturated aqueous solution of $NaHCO_3$ (or Na_2CO_3) (30 ml) stirred for 5 min and then extracted with dichloromethane (5 × 15 ml). The combined organic layers were washed twice with distilled water and dried over anhydrous Na_2SO_4. The mixture was then filtered and the solvent removed by means of rotary evaporation under reduced pressure. The products were identified according to their spectroscopic data and the results of GC analysis compared with commercially available authentic samples. 8B and 9B which are not commercial products had spectroscopic data identical to that previously published in refs 15 and 16 respectively.

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