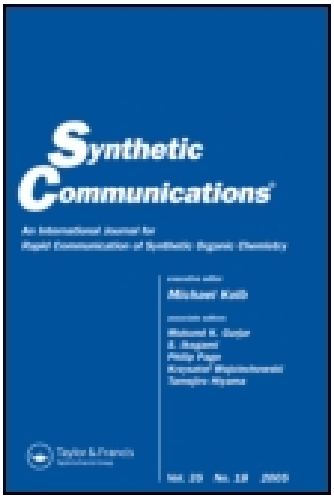

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# Mild Approach to the Deprotection of Troc from Protected Amines Using Mischmetal and TMSCl

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# MILD APPROACH TO THE DEPROTECTION OF TROC FROM PROTECTED AMINES USING MISCHMETAL AND TMSCl

**Eerold Vellemäe, Vladimir Stepanov, and Uno Mäeorg**
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***The 2,2,2-trichloroethoxycarbonyl (Troc) protecting group was efficiently removed from Troc-protected aliphatic and aromatic amines and also some Troc, Tos- and Troc, Ac-protected amines using activated mischmetal (MM). All reactions were performed by refluxing in dry tetrahydrofuran under an argon atmosphere and gave moderate to excellent yields. Several new compounds were synthesized, and new data about reactivity of Troc group were obtained.***

***Keywords***: Amines; deprotection; mischmetal; TMSCl; Troc



Protection strategies have been exceedingly useful in the synthesis of many biologically active compounds such as apratoxin A,[1] Isotaxe,[2] and aminoacridines[3] for the masking of the hydroxy- and amino groups in intermediate products. Therefore, when a reaction is to be conducted at specific site in a polyfunctional substrate, it is first necessary to block all other reactive sites by employing protecting groups that can be easily removed after the desired chemical transformation. One option is to utilize the Troc protecting group. Troc is a stable protecting group and has a relatively simple introduction method when employed for the protection of the hydroxy- and amino groups.[4] Therefore, it has been an extensively used protecting group in organic synthesis. It also allows selective stepwise cleavage[5] in the presence of an orthogonal protective group that adds to its usefulness in organic synthesis. According to the originally published Troc cleavage method,[6] which is still being actively used today, the removal is carried out via a reductive elimination process using Zn dust in 90% aqueous AcOH. Thus, the classical deprotection conditions do not allow easily reducible or acid-sensitive groups to be retained in substrates.[7] Because of this particular problem, numerous attempts to modify this method were made, where Zn has been substituted by metal pairs, such as Zn-Cu, Zn-Pb, and Cd-Pb,[8] or a less active metal than Zn.[8] However, these methods still need acidic reaction media to cleave the Troc group. In recent years, a few methods were published in which the Troc group was removed in pH-neutral conditions, for example, using

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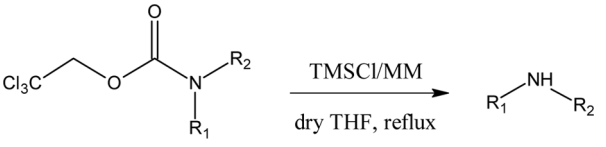
In/$NH_4Cl$ in EtOH-$H_2O$[7] mixture or using Zn-*N*-methylimidazole in ethyl acetate or acetone.[9] Also, numerous papers have been published in recent years describing lanthanoids and corresponding salts used for this purpose, including a method where $SmI_2$ in tetrahydrofuran (THF) has been applied to remove the Troc group.[4] Regardless of good yields, some of these previously mentioned methods and the reagents used for this purpose are expensive (In, $SmI_2$). Also, those procedures were applied exclusively in the absence of other well-known protecting groups such as Cbz(Z), Boc, Tos, and Ac.

However, our previous work has shown that a trimethylsilylchloride (TMSCl) and mischmetal (MM) (50% Ce, 25% La, 16% Nd, 6% Pr)[10] system works relatively fast and very selectively when applied to cleavage of the Troc protective group from hydrazines and aromatic amines without decomposition of hydrazines or Boc and Cbz groups present in the starting substrates. The aim of this research was therefore to explore those mild conditions in the presence of other well-known protecting and functional groups such as Tos, Ac, CN, and COOEt in detail (Scheme 1). Herein we report the results of our work where we utilize MM for this purpose.

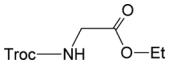
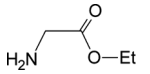
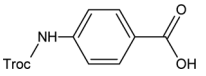
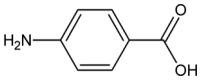
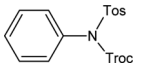
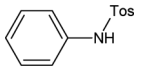
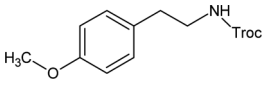
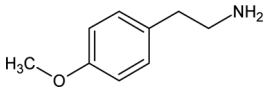
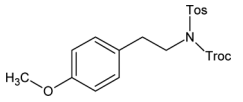
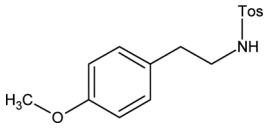
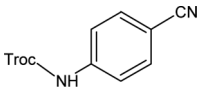
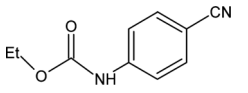
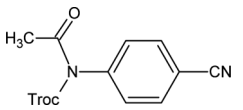
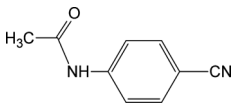
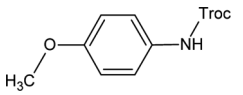
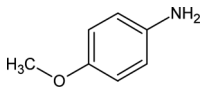
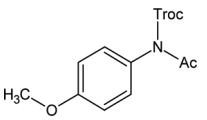
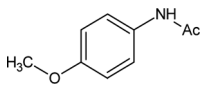
Using already optimized deprotection conditions[10] for various Troc-protected starting compounds such as aliphatic and aromatic amines and amino acids, we have applied the method to Troc,Tos- and Troc,Ac-protected amines.[11] The results of the cleavage of the Troc group from several starting compounds under optimized reaction conditions are outlined in Table 1. It shows that the reaction proceeds smoothly, yielding the corresponding deprotected products. In the course of these studies, we have confirmed that activated mischmetal in THF is capable of removing the Troc protecting group from esters and aliphatic and aromatic amines in the presence of other well-known protecting groups such as Ac and Tos or the presence of other well-known functional groups such as CN and COOEt. The cleavage of the Troc group was very selective under very mild conditions that left the ester group as well as other protecting groups in place. The behavior of MM in these conditions is interesting, because it allows the selective cleavage of the Troc group from Troc(Tos)N or Troc(Ac)N in substituted amines while the Ac and Tos groups remain unaffected. This is a very good example of the orthogonality of this new method.

During this investigation it was found that the TMSCl/MM system in THF cleaves the Troc group from p-MeO-$C_6H_4$-NH-Troc considerably faster than in the published method[7] where the Troc group was cleaved with In/$NH_4Cl$ in EtOH–$H_2O$. The reaction times were 3 and 4 h, respectively. Also, when we compared reaction speeds of p-MeO-$C_6H_4$-$(CH_2)_2$-NH-Troc and of p-Br-$C_6H_4$-$(CH_2)_2$-NH-Troc from the same work,[7] we also found that TMSCl/MM system cleaves the Troc group considerably faster than the system In/$NH_4Cl$. The reaction times for cleavage of the Troc group from those compounds were 2 and 3 h, respectively.




**Scheme 1.** $R_1$ = H, $PhCH_2$, p-HOOC-$C_6H_4$, $EtOOCH_2$, p-CN-Ph, p-MeO-$C_6H_4CH_2CH_2$, $R_2$ = H, Tos, Ac; MM = mischmetal.

**Table 1.** Deprotection of Troc group with MM/TMSCl in THF

| Entry | Compound (A) | Product (B) | Reaction time (h) | Yield (%) |
|---|---|---|---|---|
| 1[a] | Ph-$CH_2$-NH-Troc | Ph-$CH_2$-$NH_2$ | 3 | 62[e] |
| 2 |  |  | 4 | 88 |
| 3[b,c] |  |  | 24 | No reaction |
| 4[c] |  |  | 3 | 54[e] |
| 5 | Ph-NH-Troc | Ph-$NH_2$ | 2 | 92 |
| 6 |  |  | 2 | 87 |
| 7[c] |  |  | 3 | 80 |
| 8 |  |  | 8 | 60[e] |
| 9[c] |  |  | 3 | 65[d] |
| 10 |  |  | 3 | 81 |
| 11[c] |  |  | 1,5 | 52[d,e] |

[a]The identity of products (B 1, 5, 6) were confirmed by GC, and IR spectroscopy and the rest of the products were confirmed by $^1$H NMR and/or $^{13}$C NMR spectroscopy.

[b]In the reaction of number 3, 4 mmol of MM and 6.2 mmol of TMSCl were used instead of optimized conditions.

[c]New compounds (A 3, 4, 7, 9, 11) were identified by HR mass spectrometry.

[d]The yields of the products 9B and 11B were determined after purification of the crude product by column chromatography.

[e]Brine was used for washing the extract instead of distilled $H_2O$.

During this investigation, it was also discovered that the rate of cleavage of the Troc group from aliphatic or aromatic amines can be influenced by the adjacent protective group. Remarkable acceleration was observed (see Table 1, entries 8–11) if the Ac group was residing at the same nitrogen as the Troc group. It was expected

that the Tos group would also bring an acceleration effect similar to one observed in the case of the Ac protective group. Unexpectedly, instead of acceleration, deceleration actually was observed in the case of the Tos group occupying the same adjacent position (see Table 1, entries 4–7), but this discrepancy can be explained by steric hindrance of the bulky Tos group.

However, other authors[12,13] have demonstrated this acceleration effect only in the case of a Boc group, but to the best of our knowledge the impact of other protecting groups, like Ac (or Boc in our previous work[10]) on the Troc group reactivity was not reported. Usually the cleavage of the Troc group with the TMSCl/MM system took about 2 to 3 h refluxing in THF, with some significant exceptions. Thus, the cleavage of the Troc group from Troc-protected p-aminobenzoic acid in the system TMSCl/MM was not successful. Because of the possibility that substituted benzoic acid could react with MM, it therefore is not a suitable compound for those conditions. To avoid the reaction between p-aminobenzoic acid and MM, the p-aminobenzoic acid was converted into corresponding silyl esters with TMSCl in situ (using for that purpuse the known procedures[14,15]) and then proceeded to the cleavage reaction. However, even so, no desired reaction occurred after refluxing the reaction mixture with MM in dry THF for 24 h.

Another phenomenon was observed in the case of the cleavage of the Troc group from compound **9a** (see Table 1), and the reaction was ended within 3 h. We suppose that this considerable acceleration can be explained by the following factors: Ac is a strong deactivating group, and therefore it activates a corresponding nitrogen atom and brings the acceleration. Also, it is important that the Ac group has low steric hindrance, which does not hinder the interaction between TMSCl/MM and the reaction center. Indeed, it was demonstrated in our previous work[10] that a Boc group also brings the acceleration, but because of the much larger sterical hindrance of the bulky Boc group compared to the Ac group, the acceleration effect was smaller.

However, when we tried to cleave the Troc group from **8a**, which is very similar to compound **9a**, the reaction proceeded in a very different way. During this particular reaction, the TMSCl/MM system did not cleave the Troc group but instead transformed the $CCl_3CH_2O$ group into $CH_3CH_2O$. This unusual result could be explained by the fact that compound **8a** includes a cyano group in the conjugating p-position of the aromatic ring, which would reduce the reactivity of nitrogen. Also, it is important to consider the fact that all lanthanoids in MM are very active metals and in this particular case the reaction time was very long. Thus, all these factors (low activity of nitrogen, presence of active metals, and long reaction time at elevated temperatures) could be the reasons why this kind of transformation takes place. Thus, as we mentioned before, the role of an adjacent protecting group could be very important not only for the speed of the cleavage reaction but also it could significantly change the path of reaction.

In summary, we have described a new mild and cheap deprotection method for cleavage of the Troc group from various substrates using a TMSCl/MM system in dry THF. The reactions in these conditions are relatively fast and generally provide excellent yields. We also demonstrated that this deprotection method could be successfully utilized in the presence of Tos, Ac, and COOEt groups. Thus, an extremely simple, mild, cheap, and reproducible protocol is reported.

## EXPERIMENTAL

All reactions were conducted under an argon atmosphere, and all the starting compounds were confirmed by $^{1}H$ NMR and $^{13}C$ NMR spectroscopy. Column chromatography was performed using MN Kieselgel 60 (70–230 mesh).

$^{1}H$ and $^{13}C$ NMR spectra were determined on a Bruker Avance II 200 instrument operating at 200 and 50 MHz respectively, and tetramethylsilane (TMS) was used as reference.

Gas chromatography (GC) analyses were performed on an HP 5890A instrument with FID detector, using helium as carrier gas and fused silica capillary column Elite PE-5, 30 m × 0.25 mm.

High-resolution (HR) mass spectra were measured with a Thermo Electron LTQ Orbitrap ESI mass spectrometer.

Infrared (IR) spectra were measured on a Spectrum BXII (Perkin-Elmer) Fourier transform (FT)–IR spectrometer with ATR device (Zn-Se), using the KBr pellet technique.

MM was purchased from Redel-de Haen (50% Ce, 25% La, 16% Nd, 6% Pr).



### General Procedure

Freshly, manually filed MM powder (380 mg, 2.7 mmol; grain size 0.1–0.3 mm) was added to 10 ml of dry THF and activated with 0.52 ml (4.1 mmol) of TMSCl by refluxing for 30 min under an argon atmosphere. Then, 0.44 mmol of Troc-protected starting compound was added, and the obtained mixture was refluxed again. The progress of the deprotection reaction was monitored using thin-layer chromatography (TLC; EtOAc–hexane, usually 4:1 or 2:1). Before TLC, the sample was quenched with saturated $Na_2CO_3$. When the reaction was complete, the MM powder was filtered, and the resulting filtrate was neutralized with 30 ml of saturated aqueous solution of $Na_2CO_3$ (or ~10% NaOH), stirred for 5 min, and then extracted with dichloromethane (5 × 15 ml) and with EtOAc (3 × 15 ml). The combined organic layers were washed with 0.2 M citric acid aqueous solution, twice with distilled water (or brine), and then dried over anhydrous $MgSO_4$. The mixture was filtered and concentrated by rotary evaporation. If purification was needed, the crude product was purified by column chromatography.

### Preparation of Compound 9a

Compound **8a** (520 mg, 1.77 mmol) and DIPEA (N,N-diisopropylethylamine; 1.3 ml, 7.4 mmol) were added to 30 ml of acetonitrile. Then 0.5 ml (6.6 mmol) of AcCl was added, and the obtained mixture was refluxed overnight under an Ar atmosphere. The progress of the reaction was monitored using TLC (EtOAc–hexane, 2:1). When the reaction was complete, the solvent was removed on a rotary evaporator and the crude product was purified twice by column chromatography (EtOAc–hexane 1:2 and EtOAc–hexane 2:1). The collected fractions were combined and concentrated by rotary evaporation, and 250 mg of compound **9a** was obtained. The structure of the new compound was confirmed by $^{1}H$ NMR and $^{13}C$ NMR spectroscopy and HR mass spectrometry.

### Preparation of Compound 11a

The compound **11a** was prepared essentially the same way as **9a**, except that instead of DIPEA, DMAP (4-dimethylaminopyridine) was used. The yield after purification was 25%.

### Spectral Data of the Starting Compounds

**Compound 1A.** $^1$H NMR ($CDCl_3$): $\delta = 4.41/4.44$ (d, 2H, Ph-$CH_2$), 4.76 (s, 2H, $CH_2$, Troc), 5.33 (s, 1H, NH, Bn-NH), 7.31–7.33 (m, 5H, Ph). $^{13}$C NMR ($CDCl_3$): $\delta = 45.6$ (Ph-$CH_2$), 74.9 ($CH_2$, Troc), 95.7 ($CCl_3$, Troc), 127.6, 127.8, 128.9, 137.9 (Ar), 154.7 (C=O, Troc).

**Compound 2A.** $^1$H NMR ($CDCl_3$): $\delta = 1.26/1.30/1.34$ (t, 3H, EtO), 4.00–4.29 (m, 2H, $CH_2$ EtO), 4.75 (s, 2H, $CH_2$, Troc), 5.77 (s, 1H, NH). $^{13}$C NMR ($CDCl_3$): $\delta = 13.9$ (Me, EtO), 43.1 ($CH_2$, EtO), 61.5 ($CH_2$-N), 75.0 ($CH_2$, Troc), 95.4 ($CCl_3$, Troc), 154.1 (C=O, Troc), 169.2 (C=O, COOEt).

**Compound 3A.** $^1$H NMR ($CDCl_3 + d_6$-DMSO): $\delta = 4.86$ (s, 2H, $CH_2$, Troc), 7.47 (s, 1H, NH), 7.61/7.65 (d, 2H, Ar), 7.95/7.99 (d, 2H, Ar), 9.79 (s, 1H, COOH). $^{13}$C NMR ($CDCl_3 + d_6$-DMSO): $\delta = 74.5$ ($CH_2$, Troc), 95.7 ($CCl_3$, Troc), 118.3, 125.8, 130.8, 142.5 (Ar), 151.9 (C=O, Troc) 167.9 (C=O, COOH). FTIR $\nu$ ($cm^{-1}$): 3300–2500 (COOH), 1530 NH (NH-Troc), 1716 (C=O, COOH), 1674 (C=O, Troc), 1222 (C-O-C), 718 (C-Cl). Mp = 226–228 °C. $C_{10}H_8Cl_3NO_4$ $M^+ + H$ calc. 313.95622; $M^+ + H$ found 313.95697.

**Compound 4A.** $^1$H NMR ($CDCl_3$): $\delta = 2.47$ (s, 3H, Me, Tos), 4.65 (s, 2H, $CH_2$, Troc), 7.27–7.47 (m, 7H, Ar), 7.92/7.97 (d, 2H, Ar). $^{13}$C NMR ($CDCl_3$): $\delta = 21.6$ (Me, Tos), 75.7 ($CH_2$, Troc), 94.1 ($CCl_3$, Troc), 129.2, 129.6, 129.7, 135.6, 136.0, 145.3, 150.9 (Ar), 153.2 (C=O, Troc). FTIR $\nu$ ($cm^{-1}$): 1734 (C=O, Troc), 1383, 1170 ($SO_2$, Tos), 1289 (C-O-C), 713 (C-Cl). Mp = 110–112 °C. $C_{16}H_{14}Cl_3NO_4S$ $M^+ + H$ calc. 421.97819, $M^+ + H$ found 421.97812.

**Compound 5A.** $^1$H NMR ($CDCl_3$): $\delta = 4.83$ (s, 2H, $CH_2$, Troc), 6.94 (s, 1H, NH), 7.11–7.41 (m, 7H, Ar). $^{13}$C NMR ($CDCl_3$): $\delta = 74.6$ ($CH_2$, Troc), 95.3 ($CCl_3$, Troc), 119.1, 124.2, 129.2, 137.0 (Ar), 155.1 (Ar-N), 155.4 (C=O, Troc).

**Compound 6A.** $^1$H NMR ($CDCl_3$): $\delta = 2.74$–$2.81$ (m, 2H, Ph-$CH_2$), 3.39–3.49 (m, 2H, $CH_2$-NH), 3.79 (s, 3H, $CH_3O$), 4.71 (s, 2H, $CH_2$, Troc), 5.19 (s, 1H, NH), 6.82–7.13 (m, 4H, Ar). $^{13}$C NMR ($CDCl_3$): $\delta = 35.3$ (Ph-$CH_2$), 42.9 ($CH_2$-NH), 55.4 ($CH_3O$), 74.8 ($CH_2$, Troc), 95.8 ($CCl_3$, Troc), 114.5, 129.8, 130.6, 154.7 (Ar), 158.3 (C=O, Troc). Mp = 89–91 °C. $C_{19}H_{20}Cl_3NO_5S$ $M^+ + H$ calc. 482.01710; $M^+ + H$ found 482.01743.

**Compound 7A.** $^1$H NMR ($CDCl_3$): $\delta = 2.43$ (s, 3H, Me, Tos), 3.02/3.06/3.10 (t, 2H, Ph-$CH_2$), 3.79 (s, 3H, $CH_3O$), 4.02–4.10 (m, 2H, $CH_2$-NH), 4.70 (s, 2H, $CH_2$, Troc), 6.83–6.87 (m, 4H, Ar), 7.17–7.32 (m, 4H, Ar), 7.82–7.86 (m, 4H, Ar). $^{13}$C NMR ($CDCl_3$): $\delta = 21.5$ (Me, Tos), 35.8 (Ph-$CH_2$), 49.3 ($CH_2$-NH), 55.4 ($CH_3O$), 76.1 ($CH_2$, Troc), 94.5 ($CCl_3$, Troc), 114.5, 128.6, 129.5, 130.1, 136.8, 144.9, 151.2,

(Ar), 159.0 (C=O, Troc). FTIR $\nu$ ($cm^{-1}$): 1750 (C=O, Troc), 1250 (C-O-C), 1358, 1165 ($SO_2$, Tos), 714 (Cl). Oil.

**Compound 8A.** $^1H$ NMR ($CDCl_3$): $\delta = 4.84$ (s, 2H, $CH_2$, Troc), 7.36 (s, 1H, NH), 7.59–7.62 (m, 4H, Ar). $^{13}C$ NMR ($CDCl_3$): 75.0 ($CH_2$, Troc), 95.0 ($CCl_3$, Troc), 107.6 (CN), 118.5, 118.9, 133.5, 141.4 (Ar), 151.1 (C=O, Troc).

**Compound 9A.** $^1H$ NMR ($CDCl_3$): $\delta = 2.71$ (s, 3H, $CH_3$, Ac), 4.74 (s, 2H, $CH_2$, Troc), 7.28/7.32 (d, 2H, Ar), 7.72/7.76 (d, 2H, Ar). $^{13}C$ NMR ($CDCl_3$): 26.3 ($CH_3$, Ac), 75.6 ($CH_2$, Troc), 94.1 ($CCl_3$, Troc), 112.0 (CN), 117.9, 129.7, 133.0, 141.2 (Ar), 151.1 (C=O, Troc), 172.0 (C=O, Ac). FTIR $\nu$ ($cm^{-1}$): 2234 (CN), 1752 (C=O, Troc), 1716 (C=O), 1238 (C-O), 714 (C-Cl). Mp = 58–60 °C. $C_{12}H_9Cl_3N_2O_3$ $M^+ + H$ calc. 334.97515: $M^+ + H$ found 334.97495.

**Compound 10A.** $^1H$ NMR ($CDCl_3$): $\delta = 3.79$ (s, 3H, $CH_3O$), 4.81 (s, 2H, $CH_2$, Troc), 6.84–6.89 (m, 2H, Ar), 7.26 (s, 1H, NH), 7.30/7.34 (d, 2H, Ar). $^{13}C$ NMR ($CDCl_3$): 55.5 ($CH_3O$), 74.6 ($CH_2$, Troc), 95.4 ($CCl_3$, Troc), 114.5, 121.1, 130.1, 152.0 (Ar), 156.6 (C=O, Troc).

**Compound 11A.** $^1H$ NMR ($CDCl_3$): $\delta = 2.63$ (s, 3H, $CH_3$, Ac), 3.82 (s, 3H, $CH_3O$) 4.74 (s, 2H, $CH_2$, Troc), 6.91/6.95 (d, 2H, Ar), .05/7.09 (d, 2H, Ar). $^{13}C$ NMR ($CDCl_3$): 26.4 ($CH_3$, Ac), 55.5 ($CH_3O$), 75.4 ($CH_2$, Troc), 94.5 ($CCl_3$, Troc), 114.5, 129.4, 129.9, 152.8 (Ar), 159.4 (C=O, Troc), 172.6 (C=O, Ac). FTIR $\nu$ ($cm^{-1}$): 1742 (Troc), 1719 (C=O, Ac), 1246 (C-O-C), 721 (C-Cl). Mp = 51–52 °C. $C_{12}H_{12}Cl_3NO_4$ $M^+ + H$ calc. 339.99047, $M^+ + H$ found 339.99033.

$^1H$ and $^{13}C$ NMR spectral data of **1A**,[16] **2A**,[17] **5A**,[18] **6A**,[19] **8A**,[7] and **10A**[7] were identical to previously published publications.

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