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A mild method for cleavage of *N*-Tos protected amines using mischmetal and $TiCl_4$

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Abstract

The *para*-toluenesulfonyl (Tos) protecting group is removed efficiently and quickly under neutral conditions from the corresponding protected primary and secondary amines using mischmetal in moderate to excellent yields.

Keywords: Amines; Mischmetal; $TiCl_4$; Tos; Deprotection

1. Introduction

Sulfonamides, including *para*-toluenesulfonamide, are one of the most stable and widely used protecting groups[1] for reactive NH groups in organic synthesis. This group is stable under various experimental conditions such as catalytic hydrogenation and treatment with acids, bases or reductants commonly used for the removal of other protecting groups. This stability contributes to its usefulness, but also makes it difficult to remove.[2]

Most often, to remove the Tos protecting group, a solution of metallic sodium or, alternatively, a solution of lithium in liquid ammonia is necessary.[3,4] Consequently, with such drastic conditions being used, serious side reactions have been reported and the yields of regenerated compounds with free NH group(s) are sometimes poor.[5] The Tos group has also been cleaved by employing $NaAlH_2(OCH_2CH_2OCH_3)$ or $LiAlH_4$ in toluene.[6] Another widely used strategy for cleavage of the Tos group is based on acid hydrolysis, however, this requires a high concentration of mineral acid at elevated temperatures for extended periods of time. These approaches include HBr and P,[7] $HClO_4$ in AcOH,[8] HF–pyridine in anisole,[9] 48% HBr and phenol and 30% HBr in AcOH.[10]

Thus, classical deprotection methods requiring harsh reaction conditions cannot be considered as convenient for cleavage of the Tos group. To prevent side reactions, several new methods have been reported in recent years wherein the Tos group has been cleaved under mild conditions using the following approaches: Li–naphthalenide in THF,[11] Li and di-*t*-butylbiphenyl in THF,[12] Na in IPA,[13] Mg in MeOH with sonication,[14] Na(Hg) in MeOH[15] and $Li/TiCl_3$ in THF.[16]

Most of these methods still utilize alkali metals or highly reactive compounds such as $LiAlH_4$, which do not tolerate molecules that include easily reducible moieties. Moreover, to complete the deprotection reaction without significant formation of side products, these methods typically require cooling of the reaction mixture—Li–naphthalenide or Li with di-*t*-butylbiphenyl in THF, need to be cooled to -78 °C;[11] alternatively, they need high temperatures and/or long reaction times to accomplish the deprotection. For example, when using $NaAlH_2(OCH_2CH_2OCH_3)$ for Tos cleavage, the reaction requires approximately 20 h at reflux in toluene.[6] Some of the recently reported methods allowing removal of the Tos group at room temperature require long reaction times for complete cleavage. For example, when using Li and $TiCl_3$ in THF it takes

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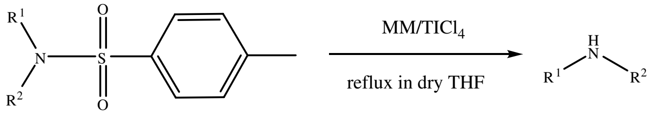
approximately 18 h in THF at room temperature.[16] Another method that allows rapid removal of the Tos group at room temperature has also been reported.[14] However, this procedure can only be used when another activating protecting group like Boc, Z or Ac is present at the same nitrogen and does not work with simple Tos-protected aromatic and aliphatic amines.[14,17] Recently, numerous papers have been published where lanthanides and their salts have been adapted for use in organic synthesis,[18] including Tos group cleavage.[19] Regardless of the good yields with some of the previous methods, some reagents employed are rather expensive (SmI_2)[19] or toxic (Na/Hg).[15]

Thus, the aim of our work was to find a fast, safe, cheap and easily reproducible method for removing the Tos group from the corresponding protected amines, hydrazines and amino acids under mild conditions. Herein, we report the results of our work where we utilize mischmetal (MM), (50% Ce, 25% La, 16% Nd, 6% Pr)[18] for this purpose (Scheme 1).

As the first step of optimization of this process, we applied the same reaction conditions reported in our previous work.[18] However, the results were not satisfactory because the deprotection reaction usually required refluxing the mixture for at least 48 h. To accelerate the reaction, the influence of different activators were studied, for example, $TiCl_4$, $SnCl_4$ and 1,2-dibromoethane. The most efficient Tos group cleavage was observed when approximately 6 equiv of mischmetal and 4.9 equiv of $TiCl_4$ were used (Table 1, entry 10).



$R^1 = p\text{-}CH_3O\text{-}C_6H_4$, *n*-Bu, Ph, Ph-NH, Ph-$CH_2$, $p\text{-}MeO\text{-}C_6H_4\text{-}CH_2\text{-}CH_2$, L-Pro
R^2 = H, Boc, Troc, Me, *n*-Bu

Scheme 1.

Having optimized the deprotection conditions, various Tos-protected aromatic amines, aliphatic amines, hydrazines and amino acids were prepared according to modified methods published previously[20] and subjected to the deprotection reaction using the conditions described above (Table 1, entry 10). The results are outlined in Table 2. It can be seen that the reaction proceeded smoothly to furnish the corresponding amines or other compounds generally, in good to excellent yields.

When employing the MM/$TiCl_4$ system Tos group cleavage proceeded usually within 3–4 h at reflux in THF. Another very important advantage of this method is that MM/$TiCl_4$ enables Tos group cleavage from non-activated or slightly activated primary and secondary aliphatic amines and also from aromatic amines under neutral reaction conditions.

We found that the activated mischmetal in THF was capable of removing the Tos group in the presence of other common functional groups such as MeO and Ph. However, the cleavage was not very selective. When other widely used protecting groups, such as Boc, Troc, Z (Cbz) and Ac (Table 1) were present, those groups were also removed under our reaction conditions.

We also discovered that it was possible to accelerate cleavage of the Tos group from aromatic amines in two ways. Acceleration was observed if the aromatic ring included an electron donating group, such as MeO or if the same nitrogen atom was bonded to a strong electron-withdrawing group, such as Boc or Troc (Table 2, see entries 3–5). Thus, it should be possible to increase the rate of the cleavage even further if more potent electron-withdrawing groups are present.

The behaviour of mischmetal under these conditions is interesting. Considering that the Tos group is generally

Table 1
Optimization of the reaction conditions[a]

Entry	Compound	Time (h)	Activator (equiv)	Product	Conversion[c] (%)
1	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH\text{–}Tos$	5	TMSCl (9.3)	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH_2$	<10
2	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH\text{–}Tos$	48	TMSCl (18.2)	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH_2$	>90
3[b]	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH\text{–}Tos$	24	TMSCl (18.2)	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH_2$	0
4	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH\text{–}Tos$	5	TMSCl, $Br\text{–}CH_2\text{–}CH_2\text{–}Br$ (6.1; 5.2)	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH_2$	Traces
5	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH\text{–}Tos$	24	$Br\text{–}CH_2\text{–}CH_2\text{–}Br$ (5.2)	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH_2$	0
6	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH\text{–}Tos$	4	$TiCl_4$, $Br\text{–}CH_2\text{–}CH_2\text{–}Br$ (4.1; 5.2)	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH_2$	0
7	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH\text{–}Tos$	4	$SnCl_4$ (3.9)	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH_2$	0
8	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH\text{–}Tos$	4	$TiCl_4$ (2.1)	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH_2$	50
9	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH\text{–}Tos$	4	$TiCl_4$ (4.1)	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH_2$	>90
10	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH\text{–}Tos$	2.5	$TiCl_4$ (4.9)	$p\text{-}CH_3O\text{–}C_6H_4\text{–}NH_2$	>99
11	Boc–NH–NH–Tos	3	$TiCl_4$ (4.9)	—	Dec.[d]
12	*Z*-NH–NH–Troc	3	$TiCl_4$ (4.9)	—	Dec.[d]
13	*n*-Bu–NH–Tos	1.5	$TiCl_4$ (4.9)	*n*-Bu–NH_2	<99
14	Ph–NH–Ac	1.5	$TiCl_4$ (4.9)	Ph–NH_2	<99
15	Ph–NH–Ac	24	$TiCl_4$:H_2O (4.9:1)	Ph–NH_2	0

[a] All reactions were performed at reflux in dry THF under argon atmosphere and 6.1 equiv of MM was used.
[b] In entry 3, 1,4-dioxane was used instead of THF.
[c] Extent of conversion was monitored by TLC.
[d] The product decomposes.

Table 2
Deprotection of the Tos group with mischmetal/$TiCl_4$ in dry THF

Entry	Starting material[a]	Reaction time (h)	Product	Yield[b] (isolated) (%)
1	Ph–NH–NH–Tos	3	Ph–NH–NH_2	23
2	Ph–NH–Tos	8	Ph–NH_2	99
3	Ph–*N*(Boc)–Tos	5	Ph–NH_2	50[c]
4	Ph–*N*(Troc)–Tos	4	Ph–NH_2	97
5	*p*-MeO–C_6H_4–NH–Tos	2.5	*p*-MeO–C_6H_4–NH_2	80
6	Ph–CH_2–NH–Tos	3	Ph–CH_2–NH_2	23
7	Ph–CH_2–NH–Tos	3	Ph–CH_2–NH_2	40[c]
8	Ph–CH_2–*N*–(Me)–Tos	6	Ph–CH_2–NH–Me	45
9	*p*-MeO–C_6H_4–CH_2–CH_2–NH–Tos	2.5	*p*-MeO–C_6H_4–CH_2–CH_2–NH_2	40
10	(*n*-Bu)$_2$–*N*–Tos	3	(*n*-Bu)$_2$–NH	78
11	*N*-Tos-(L)proline	3	HN(L)proline	83

[a] The spectral data of the starting compounds in entries 1–11 are presented in the supplementary data.
[b] Yield after purification of the crude product by column chromatography.
[c] 5% NaCl was used for washing the extract instead of distilled H_2O.

removed via reductive elimination,[11–13] we propose that lanthanide chlorides formed during activation of the mischmetal act as mediators in the deprotection of the Tos group. The mischmetal essentially acts as an electron donor. In the presence of water, these salts can be hydrolyzed, effectively quenching the reaction. This could be the reason why the reaction must be conducted in a water-free environment (Table 1, see entry 15).

In conclusion, we have described a new, mild and cheap method for the cleavage of Tos groups by using the mischmetal/$TiCl_4$ system in dry THF. The reactions are relatively fast and typically provide high yields.

2. Experimental

General procedure: 456 mg (3.2 mmol) of freshly, manually filed mischmetal (from Redel–de Haen, for applications see Ref. 21) powder (grain size 0.1–0.3 mm) was added to 10 ml of dry THF and activated with 0.24 ml (2.18 mmol) of $TiCl_4$ by refluxing for 20–30 min under an argon atmosphere. Then Tos-protected starting material (0.53 mmol) was added and the mixture refluxed for the indicated period of time (see Table 2). The progress of the deprotection reaction was monitored by TLC (EtOAc: hexane, usually 2:1, the sample was neutralized with 2 M NaOH prior to running the TLC). When the reaction was complete, the mischmetal powder was filtered off and the resulting filtrate was neutralized with 30 ml of 2 M NaOH aqueous solution, stirred for 5 min and then extracted with dichloromethane (5 × 15 ml). The combined organic layers were washed twice with distilled water (or 5% NaCl solution) and dried over anhydrous Na_2SO_4. The mixture was then filtered and the solvent removed by rotary evaporation under reduced pressure. The products were identified using GC and NMR.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.098.

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