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# Novel Amine Chemistry Based on DMAP-Catalyzed Acylation

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## Background

4-(Dimethylamino)pyridine (DMAP) is a good example of a modern low-molecular organic catalyst with a powerful effect on many reactions including acylations on nitrogen[1] as well as oxygen and carbon.[2] Kinetic measurements have shown that benzoylation of 3-chloroaniline in benzene at 25 °C proceeds nearly 4 orders of magnitude faster in the presence of DMAP compared to pyridine,[1] which for a long time was considered the solvent of choice in difficult acylations. Although somewhat more active catalysts of this type are nowadays available, the use of DMAP is preferred in most cases, due to its reasonable price and good availability. This account deals mainly with some recent preparative applications of DMAP to making simple new derivatives of amines and/or improving methods for the synthesis, protection, and cleavage of such. For more comprehensive reports on work involving this catalyst, including also many additional types of products, the reader is referred to some already published reviews.[3]

Introduction of substituents selectively and quantitatively on a nitrogen atom often requires application of forcing conditions, in which case side-reactions easily occur. In order to eliminate such or keep them at an absolute minimum, our approach involves complete blocking of all similar reaction sites, i.e., the manipulation of various protective groups, and we strongly advocate the application of dual protection of all amine nitrogens in this context. Invariably, DMAP has made it possible to accomplish this type of amine protection.

Several years ago, when we were occupied with a derivative of pyrrole-2-carboxylic acid (**1**) and wanted to convert it to an amide,[4] we instead obtained the corresponding cyclic dimer **2**, known previously as a pyrocoll[5] (Scheme 1). To avoid this type of side-product, it was obvious that the NH function of **1** had to be protected, but this turned out to be difficult because standard methods for introduction of amino-protective groups such as Boc (*tert*-butoxycarbonyl),[6] originally applied in peptide synthesis, did not give satisfactory results with pyrroles. Influenced by a paper by Bohlmann et al.,[7] in which the authors acetylated a number of pyrroles and indoles in 73-91% yields with a small excess of acetic anhydride in the presence of 1 equiv of DMAP *at room temperature*, we decided to attempt to make Boc-pyrrole with di-*tert*-butyl dicarbonate ($Boc_2O$) along a similar line. In this context we developed an optimized procedure to such Boc compounds based on the use of a *catalytic* amount of DMAP without extra base,[8] which was subsequently applied also for the synthesis of $N^{in}$-Boc-protected tryptophan and peptides thereof.[9]

Independently of our work dealing with protection of pyrroles and indoles, Grieco et al. introduced Boc as a protective group for N-substituted *amides* **3** including lactams (Scheme 2).[10] The primary products **4**, which were obtained with *stoichiometric* amounts of DMAP and additional amine in 78−96% yield as described by Bohlmann et al., have very interesting properties and can be cleaved (the lactams opened) by hydrolysis or methanolysis to give the corresponding acids ($R^3 = H$) or esters ($R^3 = Me$) **5** and Boc-protected amine **6**, from which the free amine can easily be recovered by treatment with acid. Although those novel reactions are potentially very useful, to our knowledge these authors have not reported further on this topic.[11]

Reactions like those discussed so far are very simple to perform and also to monitor, since they are accompanied by carbon dioxide evolution. Since already many years ago Guibé-Jampel and Wakselman[12a] isolated the Boc-DMAP complex **7a** as tetrafluoroborate salt ($X = BF_4$) from $Boc_2O$ and DMAP tetrafluoroborate, other authors postulated that in the presence of DMAP, $Boc_2O$ is partly converted to a corresponding complex **7b** ($X = OCO\text{-}O^tBu$), a species which was finally also identified by Knölker et al. spectroscopically (Scheme 3).[12b] DMAP obviously functions as a good leaving group, and, due to the escape of the carbon dioxide formed, the reaction is irreversible. As long as there is any $Boc_2O$ left, more **7b** can be regenerated from liberated DMAP, generally driving the reaction to completion.

In one case when $Boc_2O$/DMAP was used to make a 2,5-disubstituted pyrrolidine, a derivative was isolated which was best rationalized as formed by intermediate **7c** instead (Scheme 4).[12c]

## Novel Applications

We have also prepared a large number of Boc derivatives of N-substituted carboxamides and have also shown in

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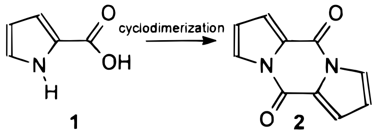
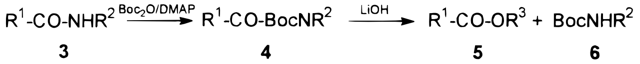
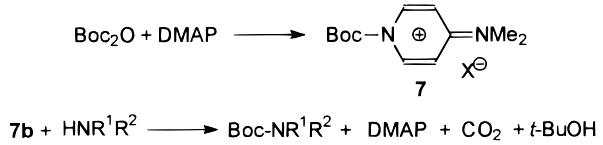
**Scheme 1**



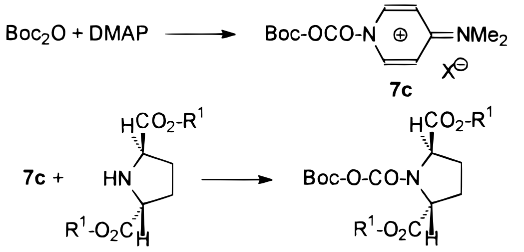
**Scheme 2**



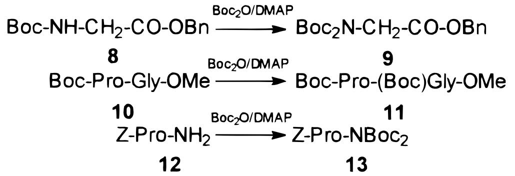
**Scheme 3**



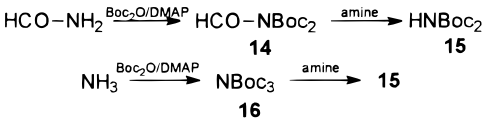
**Scheme 4**



**Scheme 5**



**Scheme 6**



that context that a few other similar types of compounds give rise to analogous derivatives.[13a,b] Thus *tert*-butyl and benzyl carbamates and N-substituted sulfon-, sulfen-, and phosphorylamides were found to undergo the same reaction and form di-*tert*-butyl and benzyl *tert*-butyl imidodicarbonates and *tert*-butyl sulfonyl-, sulfenyl-, and phosphorylcarbamates, respectively, but also a CH-acidic malonate reacted essentially quantitatively, although more slowly.[13b] Imidodicarbonate formation was first noticed as a side-product in the preparation of a derivative of $N^{\mathrm{in}}$-Boc-tryptophan.[13a] Under the influence of the DMAP, with 1 equiv of $Boc_2O$ present, there is a very clean chemoselective reaction at the indole nitrogen, but with an excess of this reagent, $N^{\alpha}$-carbamate protected tryptophan esters also react at the remaining NH. Once this had been noticed, we could also demonstrate that $Boc_2O$/DMAP can react with peptide bonds and substitute both NHs in unsubstituted amides as exemplified for compounds **8**, **10**, and **12** (Scheme 5).

Benzyloxycarbonyl (Z) and Boc are standard N-protecting groups for amino acids in peptide synthesis,[14] but $Boc_2$- and BocZ-amino acids had not been prepared up to then. The first $Boc_2$-amino acids could in principle be prepared like **9**, followed by cleavage of the benzyl ester by catalytic hydrogenolysis, although for bulky side chains smaller ester groups were required.[15a,b] BocZ-amino acids could be made from Z-amino acid esters, but in this case a carboxyl protecting group not requiring catalytic hydrogenolysis for its cleavage was needed. Although the novel N,N-bisprotected amino acids could be used for synthesis of small peptides by the active ester and carbodiimide methods,[15a,b] they reacted significantly more sluggishly than their N-monoprotected counterparts. However, as Savrda and Wakselman and Carpino and associates have later shown, these shortcomings can essentially be overcome, without accompanying racemization, by conversion instead to the more reactive fluorides.[16] Furthermore, N,N-bis-protected amino acids are useful in the synthesis of N-protected carboxy anhydrides[16a] and in cases when the presence of an acidic NH function would interfere in a synthetic sequence.[17] More recently, *N*,*N*-$Adoc_2$-amino acids (Adoc = 1-adamantyloxycarbonyl) have also been prepared and applied in peptide synthesis.[15c] In this case we found it more convenient to use the corresponding tricarbonate instead of $Adoc_2O$.[18] The synthetic utility of compounds like **9** and **13** will be further exemplified below.

With respect to the cleavage of N-substituted amides, Grieco et al.[10] have shown that the corresponding Boc derivatives **4** with $R^1$ = Bz or phenylacetyl are hydrolyzed with 3 equiv of LiOH at *room temperature* in isolated yields of 83 and 91% and methanolyzed with 2.2 equiv of NaOMe at 0 °C within 25 min in yields of 94−96%. For the hydrolysis of **3** ($R^1$ = Ac), heating with 85% hydrazine for 15 h and ($R^1$ = Bz) reflux with 6 N HCl for 48 h is recommended,[19] which clearly demonstrates the dramatically labilizing effect of the Boc group in compounds of this type. This strategy can be recommended for the removal of *N*-formyl and *N*-acetyl protecting groups, although we prefer to cleave the corresponding products **4** by aminolysis.[13c,d] As an example, *N*-formyl groups can even be cleaved by such weak bases as morpholine at *room temperature*,[13d] and such a cleavage will be illustrated in the next paragraph. Acetyl- and benzoylamino acid esters have recently been converted to the corresponding Boc derivatives by this approach.[20]

Di-*tert*-butyl imidodicarbonate (**15**) was first prepared by Carpino in modest yield according to a difficult scheme from *tert*-butyl oxalyl hydrazide via a Curtius rearrangement of the corresponding azide and subsequently alkylated on nitrogen.[21a,b] Jones et al. reproduced Carpino's results and also developed an alternative procedure involving lead tetraacetate oxidation of *tert*-butyl oxamate and reaction of the intermediary isocyanate with *tert*-butyl alcohol.[21c] We have elaborated two simple procedures for the synthesis of **15**. The first one starts from formamide and the second one from ammonia or ammonium chloride (Scheme 6). With 2 or more equiv of $Boc_2O$, forma-

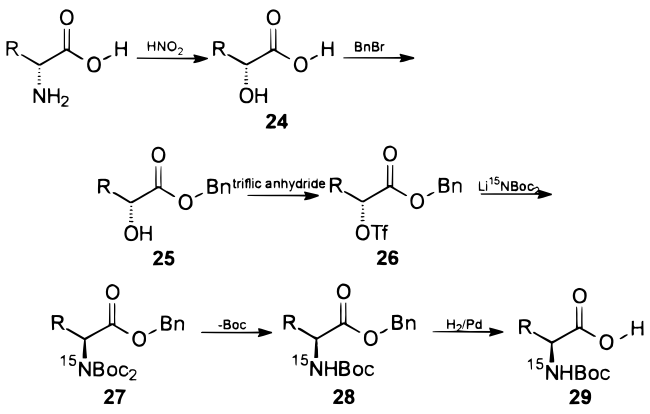
**Scheme 7**

$$\mathbf{15} \xrightarrow{R^1X} \underset{\mathbf{17}}{R^1NBoc_2} \xrightarrow{-Boc} \underset{\mathbf{18}}{R^1NHBoc} \xrightarrow{R^2X} \underset{\mathbf{19}}{R^1R^2NBoc} \xrightarrow{-Boc} \underset{\mathbf{20}}{R^1R^2NH}$$

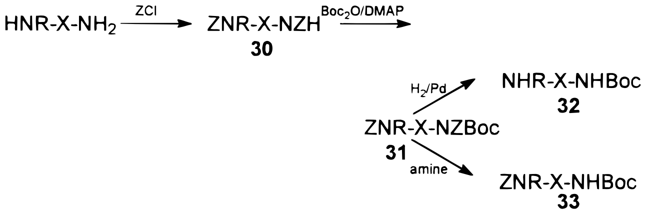
**Scheme 8**

$$Boc_2{}^{x}NK + Br\text{-}{}^{y}CH_2\text{-}{}^{z}CO\text{-}OEt \longrightarrow \underset{\mathbf{21}}{Boc_2{}^{x}N\text{-}{}^{y}CH_2\text{-}{}^{z}CO\text{-}OEt} \xrightarrow{TFA} \underset{\mathbf{22}}{Boc\text{-}{}^{x}NH\text{-}{}^{y}CH_2\text{-}{}^{z}CO\text{-}OEt} \xrightarrow{NaOH} \underset{\mathbf{23}}{Boc\text{-}{}^{x}NH\text{-}{}^{y}CH_2\text{-}{}^{z}CO\text{-}OH}$$

**Scheme 9**



**Scheme 10**



mide is substituted twice with Boc as in **12** to give **14**, from which the formyl can be cleaved off with a small excess of aliphatic amine in a one-pot reaction.[22a] The second procedure in principle is even simpler. With 4-5 equiv of Boc$_2$O, all the three NHs are substituted with Boc, and from the intermediate **16** one is cleaved off by *aminolysis* to give the product, also in a one-pot reaction, in nearly quantitative yield.[22b] Consequently the latter procedure is particularly suitable for the synthesis of the $^{15}$N-labeled species **15b** (95% from commercial $^{15}N$-ammonium chloride).[22b]

Compound **15** is a useful *Gabriel reagent*,[21,22a,c] the p$K_a$ of which has been determined to 16.9 in DMSO[22d] and from which the stable, nonhygroscopic potassium salt has been prepared.[21c] With two monovalent protecting groups on its nitrogen instead of one divalent group such as in phthalimide and a procedure to remove one Boc group absolutely selectively with a minute amount of acid from the alkylation product **17**,[23] it in principle allows two consecutive alkylation steps and therefore the synthesis also of *secondary* amines **20** (Scheme 7). Another excellent method to cleave off one Boc group selectively from **17** will be discussed in a different context.[24] Before we proceed to some applications of Scheme 7, it should be pointed out that the latter part of it, from **18** to **20**, has also been realized.[25]

The potassium salts of **15** and H$^{15}$NBoc$_2$ (**15b**) together with the three [$^{13}$C]labeled ethyl bromoacetates were applied to make the whole set of $^{15}$N- and/or $^{13}$C-labeled Boc-glycines (Scheme 8).[26a,b] The yields in each step were essentially quantitative as required in work with these expensive precursors and intermediates. From the intermediate **21** the protecting groups can also be removed in the reversed order, but we have found it a little more convenient to cleave off one Boc group with acid before the final ester hydrolysis of **22** is performed. Later we developed an efficient phase-transfer catalysis (PTC) alkylation directly from **15b** to **21**.[26c] Compound **23** ($x/y/z$ = 15/13/13) was used as a starting material in asymmetric synthesis of a number of proteinogenic amino acids.[27] We have also applied **15b** for the synthesis of a number of $^{15}$N-labeled Boc-L-amino acids (Scheme 9).[28] This reaction starts from commercial D-amino acids which are first converted to the corresponding hydroxy acids **24**, esterified to **25**, and converted to triflates **26**. On reaction with the lithium salt of **15b**, generated in situ with *n*-butyllithium, clean inversion to **27** takes place, from which one Boc group is removed to give **28**, as in the previous scheme, and the benzyl ester is finally cleaved by catalytic hydrogenolysis. In all experiments so far, the final products **29** exhibited a chiral purity better than 99% ee. Similar results were obtained in Mitsunobu alkylations with a more acidic reagent, ZTroc-$^{15}$NH (Troc = 2,2,2-trichloroethyloxycarbonyl).[28a]

The novel acylcarbamate and imidodicarbonate chemistry described so far also gave us a possibility to easily *discriminate* between primary and secondary amines on a preparative scale (Scheme 10).[29a,b] With a minimum of 2 equiv of a suitable protective agent for amino groups such as ZCl, first *both* the amino groups of the mixed primary/secondary diamine are protected in **30**; this is followed by reaction with 1 equiv of Boc$_2$O in the presence of catalytic amounts of DMAP, when only the originally primary amino group can react. The product **31** can be cleaved in two ways, either by catalytic hydrogenolysis to give **32**, in which the *secondary* amino group is now liberated and the *primary* amino group is protected, or by selective aminolysis which only cleaves the imidodicarbonate moiety and leaves the amino groups of **33** *orthogonally protected*. This scheme works for both aliphatic and aromatic diamines and has also been applied to spermidine. With acetyl instead of Z, via **34** and **35**, *selective deacetylation* at primary amino amino groups becomes feasible as demonstrated for **36** (Scheme 11).[29c] The additional discrimination between the two primary amino groups in spermidine requires some additional manipulation but is possible as shown in Scheme 12, which results in the selectively protected derivative **42**.[29b]

According to Ganem and co-workers,[30] in the presence of 1 equiv of formaldehyde, spermidine cyclizes selectively to the derivative **37** with one primary, one secondary, and one tertiary amino group which can be converted as described in the previous paragraph via **38** to **39**. This

**Scheme 11**

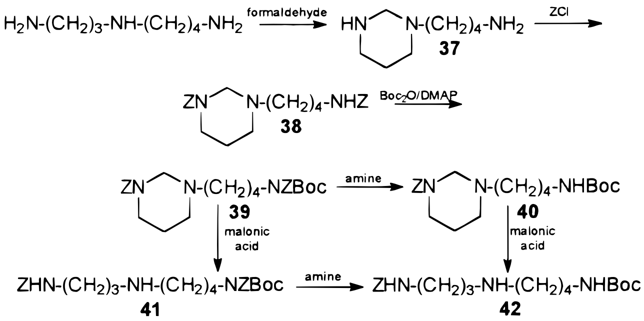
$$H_2N\text{-}(CH_2)_3\text{-}NH\text{-}(CH_2)_4\text{-}NH_2 \xrightarrow{Ac_2O}$$

$$\underset{\mathbf{34}}{AcHN\text{-}(CH_2)_3\text{-}NAc\text{-}(CH_2)_4\text{-}NHAc} \xrightarrow{Boc_2O/DMAP}$$

$$\underset{\mathbf{35}}{AcBocN\text{-}(CH_2)_3\text{-}NAc\text{-}(CH_2)_4\text{-}NBocAc} \xrightarrow{amine}$$

$$\underset{\mathbf{36}}{BocHN\text{-}(CH_2)_3\text{-}NAc\text{-}(CH_2)_4\text{-}NHBoc}$$

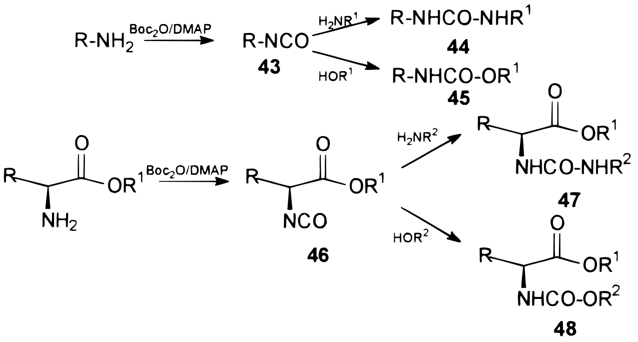
**Scheme 12**



compound can be deprotected in two different ways, either via **40** or **41**, to give the desired product **42**, in which the two primary amino groups carry orthogonal protective groups.

Knölker and co-workers have shown that primary amines with $Boc_2O$ and, preferentially, a stoichiometric amount of DMAP give rise to isocyanates **43** which for sterically hindered species can be isolated in quantitative yields.[12b] This method has the explicit advantage of avoiding the need to manipulate phosgene. The isocyanate need not necessarily be isolated but can also be reacted in situ to give with amine $R^1{-}NH_2$ directly the *unsymmetrical* urea **44**[31a] or with alcohol $R^1{-}OH$, the carbamate **45**.[31b] Subsequently the authors similarly prepared chiral isocyanates **46** and made optically pure ureas **47** (also with chiral amine substituents $R^2$) and carbamates **48** (Scheme 13).[31c]

**Scheme 13**



**Scheme 14**

$$\underset{\mathbf{51}}{PNR{-}X{-}NPBoc} \xrightarrow{\text{cathodic reduction}} \underset{\mathbf{52}}{PNR{-}X{-}NHBoc}$$

## Stability and Cleavage

To better understand the sensitivity of *N*-Boc-substituted amides to aminolysis, in cooperation with Symerský and Malon, at an early stage two of our simple compounds, **49** and **50**, were submitted to crystallographic structure

$$\underset{\mathbf{49}}{Ac\text{-}NBocPh} \qquad \underset{\mathbf{50}}{Bz\text{-}NBocPh}$$

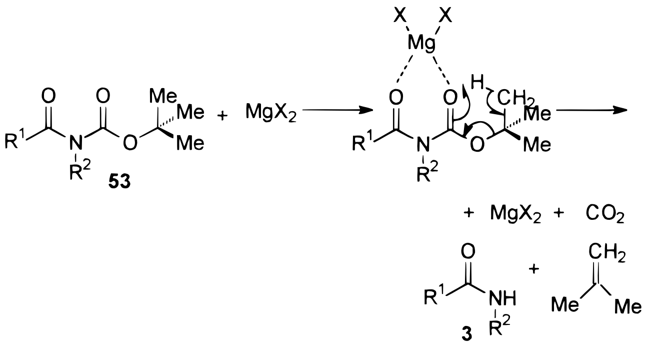
determinations.[32] These determinations showed that in **49** the sensitive Ac−N bond is increased by 0.083 Å in comparison with that in acetanilide to 1.413 Å and in **50** by 0.058 Å in relation to benzanilide to 1.403 Å. Interestingly, the Boc CO−N bonds in these derivatives are also about 0.05 Å longer than in normal Boc-amino acids. As we have seen in several cases already, the introduction of two or three acyl groups on the same nitrogen atom also affects their sensitivity to aminolysis drastically, which we employed for the deacylation of **4**,[13c,d] **14**,[22a] and **16**.[22b] Davidsen et al. have exploited the increased electrophilicity of the acyl carbon to accomplish useful transamidations.[33] In the same sense **16** could be considered a Boc-protecting agent, although we should hardly recommend it as such.

To our knowledge, Singer and Sharpless were the first to attempt to exploit this phenomenon by electrochemical methods.[34] These authors tried to lower the electrochemical cleavage potential for an N-substituted toluenesulfonamide group by introduction of electron-withdrawing substituents on its nitrogen atom and, using NaH and Boc-azide, succeeded in introducing a Boc group, which indeed lowered the cleavage potential by 0.25 V. In cooperation with Maia and associates, we have studied a number of diprotected derivatives, especially of benzylamine, by cyclic voltammetry and obtained valuable information on the topic. Also in our compounds Boc lowered the cleavage potential for tosyl by about 0.25 V but affected benzoyl significantly more, up to 0.58 V.[35a,b] This fact made it possible to cleave off both tosyl and benzoyl, abbreviated P below, selectively from **51** by cathodic reduction in mixed primary/secondary diamine derivatives on a preparative (up to 4 gram) scale[35c] (Scheme 14).

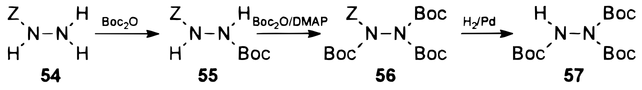
We have also studied the influence of substituents in position 4 of the benzenesulfonyl group and found that the cyano-substituted species cleaves at 0.74 V lower potential than tosyl,[35d] and since it in turn also can be converted to a *tert*-butyl sulfonylcarbamate, a further decrease in cleavage potential of 0.23 V in relation to tosyl is thereby gained. This is the background to some work with this protective group, called Cbs (Cbs = 4-cyanobenzenesulfonyl), in connection with substituted hydrazines below, in which Cbs is cleaved by mercury-activated aluminium foil very cleanly in excellent yields.[36]

As indicated briefly above under the imidodicarbonate **17**, another excellent specific method for cleavage of such compounds, based on the use of Lewis acids, has recently been described.[24] From the proposed mechanism below it is also applicable to *tert*-butyl acylcarbamates. On addition of *catalytic* amounts of magnesium salts (X = $ClO_4$ or similar species), the magnesium forms a chelate with the *tert*-butyl acylcarbamate **53**, presumably facilitat-

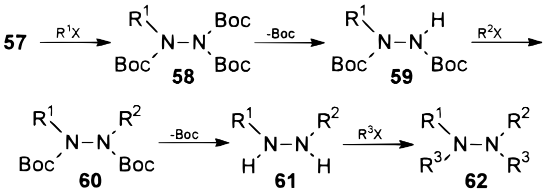
Scheme 15



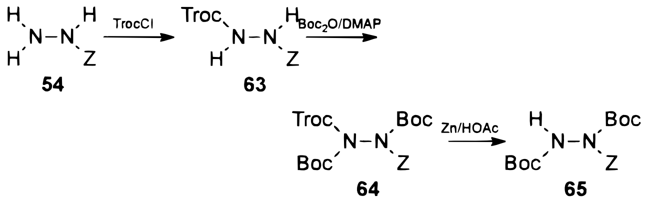
Scheme 16



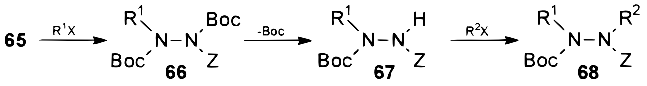
Scheme 17



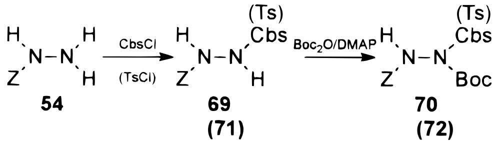
Scheme 18



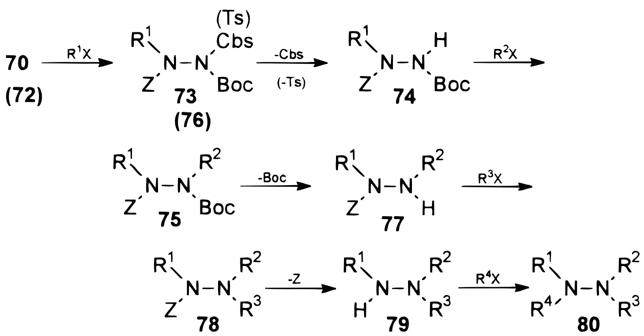
Scheme 19



Scheme 20



Scheme 21



ing hydrogen transfer from a Boc methyl group to the carbamate oxygen and initiating elimination of isobutylene. Further breakdown provides the amide or carbamate under release of carbon dioxide and recovery of the magnesium salt (Scheme 15).

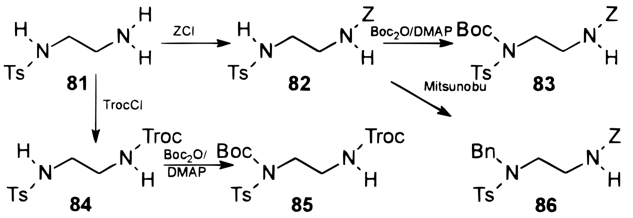
## Novel Hydrazine Derivatives

As mentioned above, in connection with our second synthesis of compound **15** we prepared and characterized also $NBoc_3$ (**16**). Previously, however, we had initiated similar work on hydrazine and shown that Boc-hydrazine could be converted into the $Boc_4$ derivative and $N,N^1$-$Z_2$-hydrazine into the $N,N^1$-$Boc_2$-$N,N^1$-$Z_2$ derivative.[37] Only more recently we have made *triprotected* hydrazines and used them in alkylation/acylation experiments to introduce various substituents on hydrazine. Our prototypical target in this context was $Boc_3$-hydrazine **57**, which was obtained as shown in Scheme 16.[38a] The synthesis of the reagent **57** started from **54** which was first reacted with $Boc_2O$ in the *absence* of DMAP to give **55** without any remaining **54**. When DMAP was added from the beginning, product **56** became contaminated with the $Boc_4$ derivative, probably due to cleavage of Z from a *N,N*-ZBoc nitrogen under the influence of basic hydrazine. After addition of DMAP, **55** quickly formed **56**, from which Z was removed by catalytic hydrogenolysis to give crystalline **57** in a high overall yield.

Reagent **57** was investigated with respect to stepwise alkylation/acylation with intermediary deprotection for synthesis of unsymmetrically substituted hydrazine derivatives (Scheme 17).[38a] In the first step, we performed the alkylations under PTC conditions and obtained a number of compounds **58** in high yields. In these one of the imidodicarbonate Boc moieties is ultralabile to acid and can be removed selectively with a minute amount of TFA to produce **59**, which can again be alkylated in the same way. However, in **60** the two Boc groups no longer differ significantly and can consequently not be removed selectively. Removal of both followed by acylation of **61** gives rise to **62** with two identical acyl groups $R^3$. In order to introduce two nonidentical acyl groups, a new reagent with orthogonal protecting groups is obviously needed.

Such a new hydrazine reagent **65** was made (Scheme 18), using the identical starting material **54**.[38b] With TrocCl, the diprotected hydrazine intermediate **63** was obtained which was exhaustively protected with Boc to **64** before it was reductively cleaved with Zn powder to the desired reagent **65** (Scheme 19). This was initially alkylated as described for reagent **57**. The alkylation product **66** was selectively and quantitatively deprotected with $Mg(ClO_4)_2$ in MeCN[24] to **67** before it was alkylated a second time to **68**. This product with the orthogonal protective groups Boc and Z can in principle be selectively deprotected as demonstrated for the intermediate **75** (Scheme 21), which had in the meantime been prepared with the help of the Cbs-hydrazine reagent **70** (Scheme 20).[38c] It should be pointed out that **69** reacts *selectively* with 1 equiv of $Boc_2O$ in the presence of DMAP; i.e., **70** is

**Scheme 22**



formed in two steps from **54** instead of three for **57** and **65**. It was alkylated under similar PTC conditions as above.

From the monoalkylated product **73** the Cbs-protecting group, as mentioned above,[36] could be cleaved by mercury-activated aluminium foil and the product **74** subsequently alkylated. In **75** the remaining protecting groups, Boc and Z, can in principle be removed in optional order, although in this case we preferred to split off Boc first (**77**) and then introduce the acyl residue R$^3$ (**78**) before finally also Z was cleaved off (**79**) by stronger acid and again acylated to the tetrasubstitituted product **80**, in which all substituents were different. Such hydrazine reagents had not previously been described.

At this stage of our work, Dr. Nyasse in our laboratory made a fortunate and unexpected discovery about the acid- and base-stable *N*-tosyl protective group, namely that as *tert*-butyl sulfonylcarbamate it can be reductively cleaved by *magnesium powder in methanol* at room temperature. To shorten the reaction time we prefer to carry out the reaction in an ultrasonic bath under which conditions the reaction is generally initiated within a few minutes and complete within 30 min.[39] This made it possible to repeat our experiments involving the efficient but considerably more expensive Cbs-hydrazine reagent **70** with the corresponding, relatively nonexpensive Ts-derivative **72** and with this compound via **76** make **74** again.[38d] The intermediates with tosyl generally are nicely crystalline compounds. We presently believe that, as long as the radicals R$^1$−R$^3$ will survive catalytic hydrogenolysis and/or strong acid for cleavage of protective groups, for the synthesis of **80**, reagent **72** is worth examining.

As a first step to a generalization of the hydrazine chemistry to aliphatic diamines we conducted a few experiments with 1,2-diaminoethane. The known tosyl derivative (**81**) was converted to **82** (Scheme 22), which like **69** and **71** could be reacted selectively with 1 equiv of Boc$_2$O in the presence of DMAP.[40] Even the corresponding Troc derivative **84** reacted selectively on its tosyl-NH and produced pure **85** directly in essentially quantitative yield. Bordwell et al. have recently shown that the conversion time for DMAP-catalyzed reaction of amides with Boc$_2$O varies dramatically with substrate acidity and established a qualitative relationship between the acidity of the substrates and their reactions rates.[41] Our data clearly demonstrate that with a limiting amount of reagent, reaction preferably takes place at the most acidic site, i.e., at the sulfonamide. On the other hand, the tosyl derivative **82** reacted relatively poorly with benzyl alcohol under Mitsunobu conditions and gave **86** in a similar yield (60%) as reported by Weinreb et al.[42] for comparable cases.

## Summary and Outlook

As repeatedly demonstrated on specific examples, dual protection of nitrogen often has a dramatic influence on the stability of the protective groups, when used in this way and not as originally intended. Although optimized for individual use, in no case so far had we any real problems to handle the stability of the novel protective groups, made up of two conventional ones, even two sets of such simultaneously. Maybe we have just been fortunate, but actually we have been able to exploit this often significant change in stability noticed in the first deprotection step of such bisprotected amine functions. The take-home message from this work is that the two groups in such a couple generally interact strongly and consequently affect each other's stability considerably. The stability of well-known protective groups consequently vary with their environment and should *no longer* be considered invariable.

The work summarized above would appear to have many applications and could easily be extended. In general, the reaction conditions used are so mild that it seems feasible to include many additional functional groups. As an example, alkylation of some protected reagents has so far been accomplished by triflates and under Mitsunobu and PTC conditions. In this way the products could serve as starting material in further work, allowing their conversion into more sophisticated target molecules. Acylation could also be extended beyond carboxylic acid derivatives, and such work is already in progress involving compound **79**.

Although in ammonia three substituents can easily be brought together very closely, one original idea behind the choice of hydrazine was that it would make it possible to add a fourth one. Although we have so far only been concerned with the principal and experimental aspects of this problem, it is obvious that it also has functional applications. One could thus introduce pharmacophoric groups into hydrazine, ethylenediamine, as well as other amines and test the resulting conjugates for biological activity.

Whereas in hydrazine presumably all substituents are brought into maximum contact with each other, in ethylene and other aliphatic diamines they will only pairwise be in close contact; otherwise these molecules will have infinite flexibility, allowing them to adapt to their environment, whatever this will be. Conversely, by the choice of more rigid diamine backbones as illustrated by various aromatic systems, not only the distance between but also the geometry of the substituents can be restricted. With a set of reagents of this type it may therefore be possible to explore complicated interactions involving macromolecules.

Whatever the outcome of work with various synthetic products such as multisubstituted diamines on different scaffolds, the fact remains that many new, very simple compounds can be made with the aid of DMAP, although we have in this Account restricted us to derivatives of amines only. Also many previously made compounds can be made more easily and faster and/or in higher yields in this way. This may be worth remembering not least in today's race for chemical diversity.

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