Protecting Groups

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Chelating Carboxylic Acid Amides as Robust Relay Protecting Groups of Carboxylic Acids and their Cleavage under Mild Conditions**

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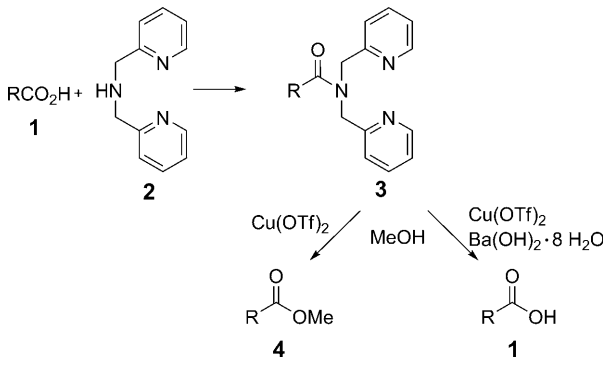
In most cases, the preparation of complex organic molecules entails the need to apply protecting groups.[1,2] Common requirements when such groups are applied to multistep synthesis are straightforward insertion, robustness to different reaction conditions, and selective cleavage, preferably with high yields and under mild conditions. In addition, a cleavage step orthogonal to that used for common protecting groups would also be desirable.

Recently, we published two new linker entities for solid-phase synthesis.[3,4] These enable the attachment of carboxylic acids to the solid phase through an amide bond and release after an unusual complexation of the amide nitrogen atom with Cu^{2+} ions followed by methanolysis. This sequence yields the methyl ester of the originally bound carboxylic acid. The release proceeded under very mild conditions at room temperature and the linker entity proved to be stable not only to base and acid but also under a wide range of different reaction conditions. Numerous modifications of the originally attached carboxylic acid were possible through the application of various reaction conditions, and we have shown that the attached acid can also serve as a starting point for multistep reaction sequences.

Our results led us to surmise that the chelating units of these linkers might be suitable as so-called relay protecting groups[1] for carboxylic acids, as outlined in Scheme 1 for bispicolylamine (bpa, **2**). By definition, in a relay deprotection a robust protecting group is transformed into a labile intermediate that participates in the cleavage process under mild conditions. To the best of our knowledge, this envisaged strategy would represent the first example of the protection of carboxylic acids as amides. Straightforward cleavage of amides is normally hampered by the large resonance energy.

According to Scheme 1 the protection process would be performed as a standard coupling reaction between the carboxylic acid **1** and bpa (**2**). After modifications by follow-up reactions, treatment with Cu^{2+} in methanol would lead to the methyl ester of the carboxylic acid (**4**). As in the linker systems mentioned above, activation for methanolysis would proceed by an unusual complexation involving the nitrogen atom of the amide bond.[5] Alternatively, methanolysis mediated by the complexation could be performed in the presence of $Ba(OH)_2{\cdot}8H_2O$,[6–8] which would then yield carboxylic acid **1** directly after acidic workup. Activation by complexation was hitherto only sparsely exploited in the realm of protecting groups, despite the fact that it would add a further degree of orthogonality to commonly used deprotection methods. Additional advantages would be the robustness of the protecting group as well as the simplicity of the approach and the very mild reaction conditions.



Scheme 1. Coupling of the bpa group and deprotection to the methyl ester (**4**) or the carboxylic acid (**1**).

To evaluate these possibilities bpa was coupled to a variety of carboxylic acids according to Scheme 1, with TBTU used as the coupling reagent.[9] Treatment of the resulting amides with $Cu(OTf)_2$ in methanol at room temperature gave the carboxylic acid methyl esters **4a–g**. Alternatively, application of $Ba(OH)_2{\cdot}8H_2O$ in combination with $Cu(OTf)_2$ in MeOH resulted in the carboxylates **1a–f** (Table 1). These carboxylates were obtained in higher yields when $Ba(OH)_2{\cdot}8H_2O$ was added directly in a one-pot reaction after cleavage of the methyl esters. All the reactions occurred in good to very high yields, thus demonstrating the potential of this relay protecting group principle. It is also noteworthy that the formation of the carboxylic acids required only 20 equivalents of $Ba(OH)_2{\cdot}8H_2O$ instead of the 400 equivalents reported in references [5–7]. The results revealed at the same time that the system was compatible with aromatic (Table 1, **a–c**), aliphatic (**d**, **e**), and amino acids (**f**, **g**).

To further investigate the versatility of the new protecting group we carried out a number of reactions under different reaction conditions (Scheme 2). These experiments indicated

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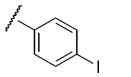
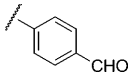
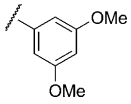
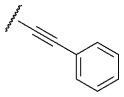
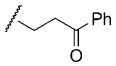
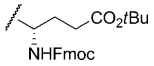
Table 1: Protection and deprotection of carboxylic acids with bispicolylamine.

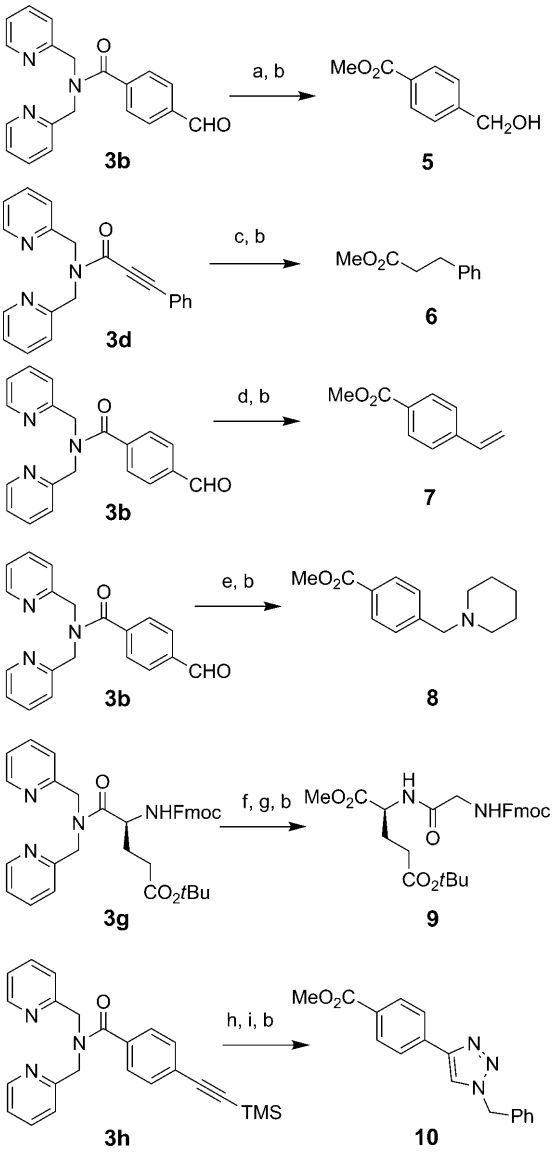
Entry	R[a]	Yield [%][b] 3	4	1
a		68	96	95
b		84	91	>99
c		65	95	72
d		95	76	90
e		>99	74[c]	87[c]
f		71	74	76
g		73	71	–[d]

[a] See Scheme 1. [b] Yield of isolated product. [c] Slow methanolysis at RT; the solution was heated at reflux for 16 h. [d] Protecting groups not compatible with the reaction conditions. Boc = *tert*-butoxycarbonyl.

that reductions are possible without affecting the protecting group (a, e). Furthermore, heterogeneous hydrogenations are possible without poisoning the catalyst (c), and copper-catalyzed reactions are possible without cleavage of the amide bond (i). In addition, the stability of the protecting group was tested under the conditions of the following reactions: Wittig olefination and reductive amination as well as peptide and click chemistry, as was demonstrated by the formation of the corresponding methyl esters, which proceeded in most cases in good to excellent yields.

In a further set of experiments 4-iodobenzoic acid was coupled to bpa to give **3a** and then the transformation to the methyl ester was evaluated in the presence of different metal salts (16 h at room temperature, Table 2). These experiments revealed that high efficiency in the methanolysis step and quantitative formation of the methyl ester was achieved with either $Cu(OTf)_2$ or $FeCl_3$. Interestingly, the degree of methanolysis was not only dependent on the nature of the metal cation, but also on the counterion, as can be seen in the strong difference between $Cu(OTf)_2$ and $CuCl_2$, with the latter giving a rather poor yield.

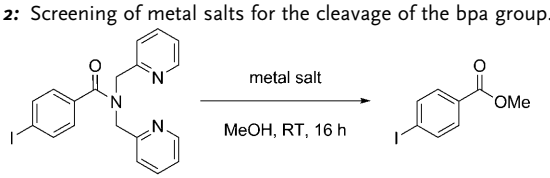
For comparison, we have carried out the same cleavage reaction with 4-iodobenzoic acid coupled to our recently published tridentate linker system on a solid support (**11a**) by using metal salts in methanol (Table 3). Similar cleavage rates were observed both in solution or on a solid phase with $Cu(OTf)_2$, $CuCl_2$, and CuCl. In contrast, cleavage to form the methyl ester proceeded nicely in solution with $ZnCl_2$ and $Zn(OTf)_2$, whereas on a solid phase virtually no cleavage could be initiated. The latter results might be an indication that different types of Zn^{2+} complexes are formed on a solid support and in solution. The investigation of this effect is a topic of ongoing research.



Scheme 2. Reagents and conditions: a) $NaBH_4$ (1.3 equiv), MeOH, RT, 10 min, 99%; b) $Cu(OTf)_2$ (1.2 equiv), MeOH, RT, 16 h, >99% (**5**); 60% (**6**); 83% (**7**); 96% (**8**); 54% (**9**); 75% (**10**); c) H_2, PtO_2 (10 mol%), EtOAc, RT, 16 h, 67%; d) $MePPh_3Br$ (2.2 equiv), KO*t*Bu (2.2 equiv), THF, −78 °C→RT, 12 h, quant.; e) $NaBH(OAc)_3$ (1.4 equiv), piperidine (1.2 equiv), 1,2-DCE, RT, 24 h, 71%; f) DMF/piperidine 4:1 (v/v), RT, 5 h, 72%; g) TBTU, DIPEA, Fmoc-glycine, DMF, RT, 12 h, 56%; h) TBAF, THF, RT, 24 h, 75%; i) $CuSO_4 \cdot 5H_2O$ (5 mol%), sodium ascorbate (10 mol%), benzyl azide (1.1 equiv), *t*BuOH/H_2O (1:1), RT, 3 d, 89%. DCE = 1,2-dichloroethane, DIPEA = *N*,*N*′-diisopropylethylamine, Fmoc = 9-fluorenylmethoxycarbonyl, TBAF = tetra-*n*-butylammonium fluoride, TBTU = 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate.

As the cleavage reaction of **3a** in solution showed quantitative conversion with both $Cu(OTf)_2$ and $FeCl_3$, we also investigated the effect of the less toxic and cheaper $FeCl_3$ (Table 4). It turned out that the rate of methanolysis at room temperature was strongly dependent on the nature of the

Table 2: Screening of metal salts for the cleavage of the bpa group.

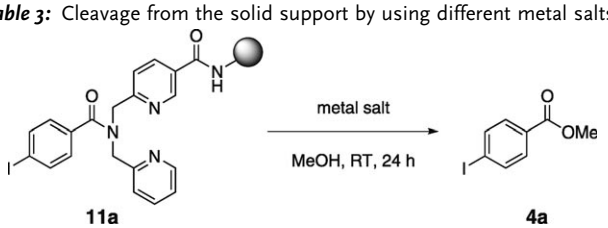


3a **4a**

Metal salt	Yield **4a** [%][a]	Metal salt	Yield **4a** [%][a]
$Cu(OTf)_2$	>99	Ag(OTf)	<1
$CuCl_2$	39		
CuCl	48	$NiCl_2$	52
$ZnCl_2$	61	$FeCl_3$	>99
$Zn(OTf)_2$	82	$Fe(OTf)_3$	14

[a] Determined by GC analysis with dodecane as the internal standard.

Table 3: Cleavage from the solid support by using different metal salts.



11a **4a**

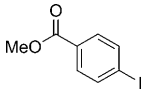
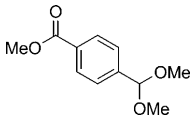
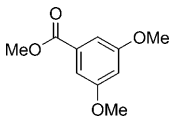
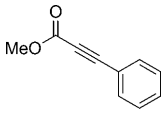
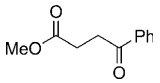
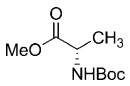
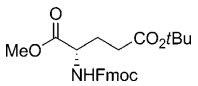
Metal salt	Yield **4a** [%][a]	Metal salt	Yield **4a** [%][a]
$Cu(OTf)_2$	93	Ag(OTf)	2
$CuCl_2$	31		
CuCl	69	$NiCl_2$	69
$ZnCl_2$	5	$FeCl_3$	35
$Zn(OTf)_2$	3	$Fe(OTf)_3$	3

[a] Determined by GC-analysis with dodecane as the internal standard.

substrate, so we decided to perform all the cleavage reactions in MeOH at reflux. Compared to $Cu(OTf)_2$, the yields of the isolated products were slightly lower, and in one case (**4f**) significantly lower. In the case of aldehyde **3b** (Table 4, **b**), the Lewis acidity of $FeCl_3$ led to the formation of the acetal. However, for large-scale procedures and for cases where the use of copper ions must be avoided, the use of $FeCl_3$ represents a useful alternative.

In summary, we have introduced chelating bispicolylamine (bpa) amides as a new relay protecting group principle for carboxylic acids. The stability of the amides towards different reaction conditions was demonstrated with several examples. The protection can be performed by using standard amide coupling reagents such as TBTU, starting from the carboxylic acid and commercially available bpa. The deprotection process occurs under very mild conditions, involves an unusual complexation of the amide nitrogen atom, and leads optionally to the carboxylic acid or its methyl ester. The conditions for cleavage are orthogonal to other known protecting groups. Since this new protecting group scheme fulfills all the general requirements for protecting groups, it should find widespread application in synthetic organic chemistry.

Table 4: Deprotection of the bpa-protected carboxylic acids **3** with $FeCl_3$ to form methyl ester **4**.[10][a]

Entry	Product **4**	Yield [%][b]
a		85
b[c]		70
c		85
d		67
e		41
f		34
g		52

[a] Reaction conditions: $FeCl_3$ (1.2 equiv), MeOH, reflux, 16 h. [b] Yield of isolated product. [c] Cleavage of **3b** is accompanied by acetalization.

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