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A Convenient, General Synthesis of 1,1-Dimethylallyl Esters as Protecting Groups for Carboxylic Acids

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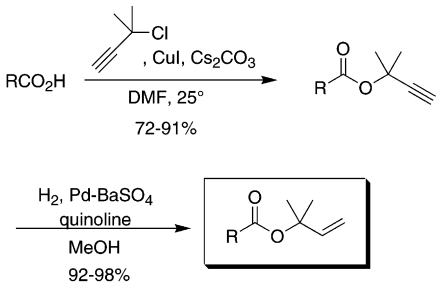
ABSTRACT



Carboxylic acids were converted in high yield to their 1,1-dimethylallyl (DMA) esters in two steps. Palladium-catalyzed deprotection of DMA esters was shown to be compatible with *tert*-butyl, benzyl, and Fmoc protecting groups, and Fmoc deprotection could be carried out selectively in the presence of DMA esters. DMA esters were also shown to be resistant to nucleophilic attack, suggesting that they will serve as alternatives to *tert*-butyl esters when acidic deprotection conditions need to be avoided.

Allyl-based protecting groups have become a popular choice for the protection of carboxylic acids, especially in peptide and glycopeptide synthesis, due primarily to the mildness and selectivity of deprotection using catalytic palladium(0).[1] Allyl-based protection strategies for the synthesis of peptides are an attractive complement to Boc- and Fmoc-based strategies for both solid- and solution-phase peptide synthesis, particularly of sensitive glyco-, nucleo-, and sulfopeptides, providing another level of "orthogonality" in biopolymer synthesis.[2]

On-resin cyclization of peptides is an important case where a combination of Fmoc and allyl protection is needed to selectively free the required carboxyl group.[3] In particular, the backbone amide linker (BAL) approach reported by Barany, Albericio, and co-workers in 1998[4a] offers a general method for preparing cyclic peptides on solid support and requires the use of a C-terminal allyl ester.[4] However, a side-reaction noted in this and other applications of allyl esters is the unwanted nucleophilic attack on the allyl ester; in the case of the BAL linker, this resulted in the unwanted formation of diketopiperazines.[5] Whereas the sterically hindered *tert*-butyl ester is known to resist nucleophilic attack, the strongly acidic conditions needed to deprotect it often preclude its use for the preparation of acid-sensitive molecules. For instance, in the case of the BAL linker, the acidic conditions needed to deprotect a *tert*-butyl ester would also result in cleavage of a substrate from the BAL linker. The logical solution is the use of a tertiary ester that can be deprotected under mild conditions. Herein, we report a general approach to the protection of carboxylic acids as 1,1-

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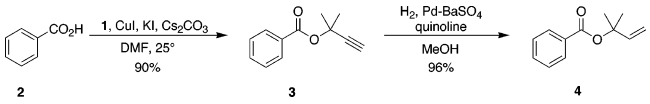
dimethylallyl (DMA) esters, which combine the mild deprotection conditions of allyl esters with the resistance to nucleophilic attack of *tert*-butyl esters.

Several previous syntheses of DMA esters have been reported,[6] but to date no general method for their synthesis from carboxylic acids has been reported. Direct synthesis of DMA esters through the esterification of 2-methyl-3-buten-2-ol proved to be impractical due to the hindered nature of the tertiary alcohol. Likewise, trapping of various 1,1-dimethyl π-allylmetal complexes with carboxylate nucleophiles gave prenyl esters rather than DMA esters due to the greater stability of the prenyl ester and kinetic preference for prenyl ester formation. Instead, the approach adopted for the synthesis of DMA esters involves the intermediacy of 1,1-dimethylpropargyl esters, which can be subsequently reduced to DMA esters. This approach was suggested to us by a copper-catalyzed synthesis of aryl propargyl ethers via nucleophilic attack on tertiary propargylic leaving groups.[7]

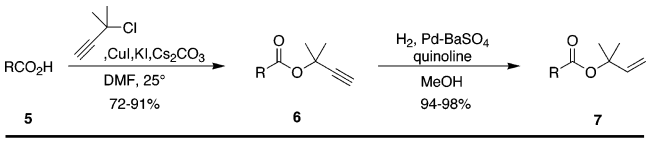
Treatment of 3-chloro-3-methyl-1-butyne (**1**) with benzoic acid in the presence of anhydrous copper(I) iodide did in fact afford the desired 1,1-dimethylpropargyl ester **3** in good yield (Scheme 1). Although initial results were obtained using

Scheme 1



K_2CO_3 as the base, use of Cs_2CO_3 as base was found to give superior results. The selectivity for formation of the tertiary ester likely results from attack of the carboxylate ion on a copper metallocumulene.[7] Partial hydrogenation of the alkyne afforded the desired DMA ester **4** in excellent yield. With the viability of this approach thus established, a series of N-protected amino acids were esterified using these conditions (Table 1). In all cases, the DMA esters were synthesized in good yield and with complete regiochemical control. Subsequent reduction by partial hydrogenation of the alkyne afforded the corresponding DMA esters in very high yields. The DMA esters of Fmoc-, Boc-, and Cbz-protected amino acids were synthesized using these conditions.

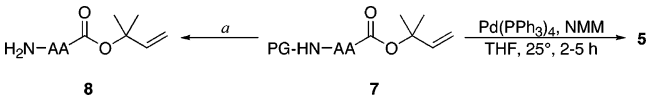
Table 1. Synthesis of DMA Esters from Protected Amino Acids



R	yield of **6** (%)	yield of **7** (%)
Fmoc-Val (**5a**)	81	96
Fmoc-Pro (**5b**)	85	96
Fmoc-Thr(Trt) (**5c**)	91	94
Fmoc-Abu (**5d**)	76	97
Fmoc-Tyr(*t*-Bu) (**5e**)	90	98
Fmoc-Orn(Boc) (**5f**)	87	96
Fmoc-Glu(*t*-Bu) (**5g**)	82	97
Fmoc-MeVal (**5h**)	79	97
Fmoc-Gly (**5i**)	88	94
Fmoc-Ala (**5j**)	89	99
Boc-Val (**5k**)	72	96
Cbz-Phe (**5l**)	82	92

With various DMA esters in hand, it remained to be seen whether the DMA ester would prove to be orthogonal to the other protecting groups. In Table 2, it is shown that both

Table 2. Selective Deprotection of DMA Ester and Fmoc Group



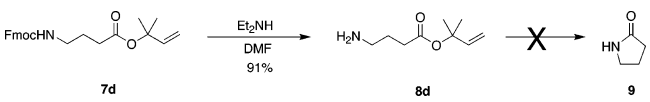
PG	AA	yield of **5** (%)	yield of **8** (%)
Fmoc	Val (**7a**)	82	93
Fmoc	Pro (**7b**)	90	73
Fmoc	Abu (**7d**)	90	70
Fmoc	Tyr(*t*-Bu) (**7e**)	91	88
Fmoc	Orn(Boc) (**7f**)	83	86
Fmoc	Glu(*t*-Bu) (**7g**)	87	92
Boc	Val (**7k**)	84	*b*
Cbz	Phe (**7l**)	93	*b*

[a] Deprotection conditions for Fmoc can be found in Supporting Information; Boc deprotection was carried out using various concentrations of TFA in CH_2Cl_2 with various acid scavengers; Cbz deprotection was carried out by hydrogenolysis over various Pd catalysts. [b] Deprotection of Boc and Cbz lacked selectivity, resulting in loss of DMA ester.

the Fmoc group and the DMA ester can be removed selectively in the presence of the other. Moreover, DMA deprotection using catalytic Pd(0) and *N*-methylmorpholine proceeded in high yield and was compatible with *tert*-butyl protection of various amino acid side chains. While DMA esters could be readily deprotected in the presence of Fmoc, Boc, and Cbz groups, neither Boc or Cbz could be selectively deprotected in the presence of a DMA ester. Thus, DMA esters should be considered orthogonal only with the Fmoc group. The competitive deprotection of a DMA ester in the presence of an alloc group was also carried out, but no significant kinetic selectivity was observed.

It is especially noteworthy that, during deprotection of the γ-amino acid Fmoc-Abu (**7d**), the liberated primary amine **8d** does not cyclize to form γ-butyrolactam **9** (Scheme 2).

Scheme 2



The fact that this normally facile reaction fails to occur under the reaction conditions suggests that, like *tert*-butyl esters, DMA esters resist nucleophilic attack under all but the most

forcing conditions. It is therefore suggested that DMA esters could successfully prevent unwanted diketopiperazine formation when using the BAL linker for peptide synthesis.

In conclusion, it has been demonstrated that carboxylic acids can be protected as their 1,1-dimethylallyl (DMA) esters in two steps. This methodology should prove to be quite general. Using this methodology, several DMA esters of different amino acids with various side chain protecting groups were prepared and selectively deprotected. The DMA ester was shown to be orthogonal to the Fmoc group and compatible with *tert*-butyl and benzyl-based protecting groups. The DMA ester should prove to be a useful alternative to the *tert*-butyl ester for acid-sensitive substrates and provide protection against nucleophilic attack on the ester carbonyl.

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Supporting Information Available: Experimental procedures and full characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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