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Alkenyl tricarbonyl derivatives of α-amino acids as trielectrophiles. Formation of heterocyclic-substituted products

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Abstract—Alkenyl tricarbonyl esters have been prepared by reaction of mono aldehydes of dibasic amino acids with tricarbonyl esters. These systems undergo reaction with diamines and other dinucleophiles by a combination of Michael addition and nucleophilic attack at the electrophilic central carbonyl to form pyrrole derivatives. These monoaldehydes may also be used to incorporate imidazole and furan residues into the amino acid starting materials. © 2002 Elsevier Science Ltd. All rights reserved.

The 1,2,3-vicinal tricarbonyl (VTC) system represents a potent electrophilic unit which has unique applicability in organic synthesis, due to the enhanced reactivity of the central carbonyl group with nucleophiles. In recent years, the chemistry of this system has been extensively explored[1–3] in connection with the synthesis of varied products of biological interest.

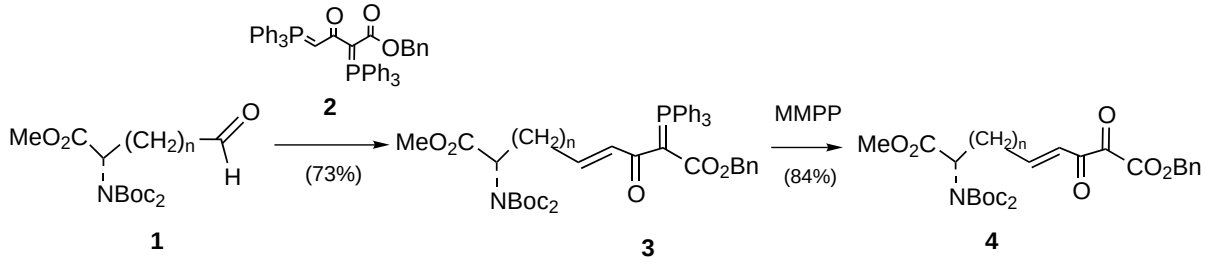
One generally useful method for forming tricarbonyl esters involves the reaction of carboxylic acids with alkyl triphenylphosphoranilidine acetates, yielding stable diacyl ylides which can readily be converted to tricarbonyl esters by oxidizing agents such as ozone. Recent work by Baldwin[4] has shown how monocarboxylic acid derivatives of protected aspartic and glutamic acids could be transformed to tricarbonyl esters by this route. The amino acids, activated in this way, were then converted to novel heterocyclic products by reactions with aromatic diamines and other dinucleophiles.

As discussed in the preceding paper,[5a] a tricarbonyl aggregate which has received particular attention incorporates the vinyl VTC ester grouping. In this and earlier work, numerous examples have been reported showing how this array may serve as an unusually versatile building block for generating structural units not readily accessible by conventional synthetic methods.[5] We now report the extension of earlier vinyl VTC studies to the reactions of alkenyl VTC esters with amines, diamines and other polynucleophiles.

In this work we followed up on earlier studies by Martin and co-workers[6] on the selective reduction (DIBAL) of aspartic and glutamic acid diesters to form monoaldehydes as reagents for Wittig reactions, yielding unsaturated derivatives of the amino acids.

These aldehydes were then used in reactions with diylides **2** previously reported by Chopard.[7] Our interests were focused on mono Wittig processes in order to generate products **3** which could lead to heterocyclic-substituted amino acids through precursors **4**.

Our reaction sequence began with the aldehyde **1**, $n=2$ prepared by the reduction of a di-Boc-protected glutamic acid dimethyl diester.[6] Wittig reaction of **1** with the bis phosphorane **2**[7] yielded the α,β-unsaturated keto



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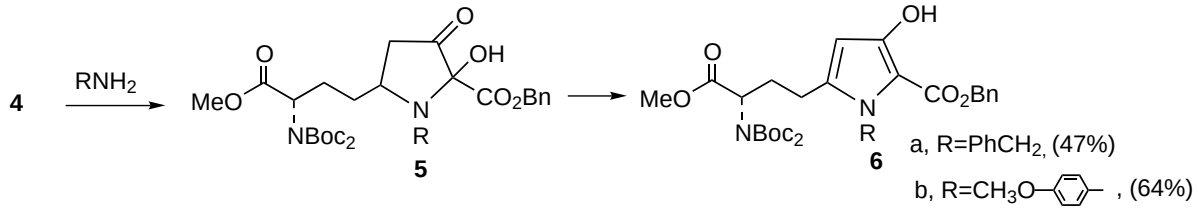
ylido ester **3**, which was then oxidized to yield the alkenyl tricarbonyl **4**. In the course of related work, we have employed a number of oxidizing agents to cleave the carbon–phosphorous double bond in ylides of this type: ozone,[8a] singlet oxygen,[8b] Oxone®[8c] or dimethyl dioxirane.[8d] In the present case, we found that magnesium monoperphthalate (MMPP)[9] gave excellent results.

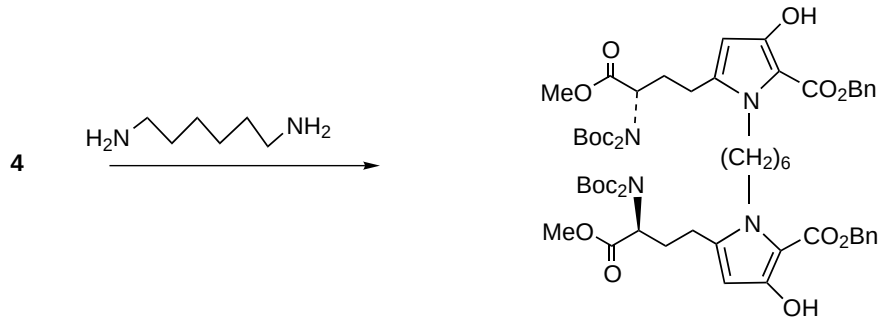
Along the lines of our earlier synthesis of prodigiosin,[10] the first use of an alkenyl tricarbonyl as a trielectrophile, we treated **4**, $n=2$ with primary amines, including benzylamine, *p*-anisidine, 1,6-diaminohexane and tryptamine. As observed in previous studies,[5b] the intermediate labile hydroxy pyrrolidone carboxylates **5** were readily converted to the stable *N*-substituted pyrroles **6**.

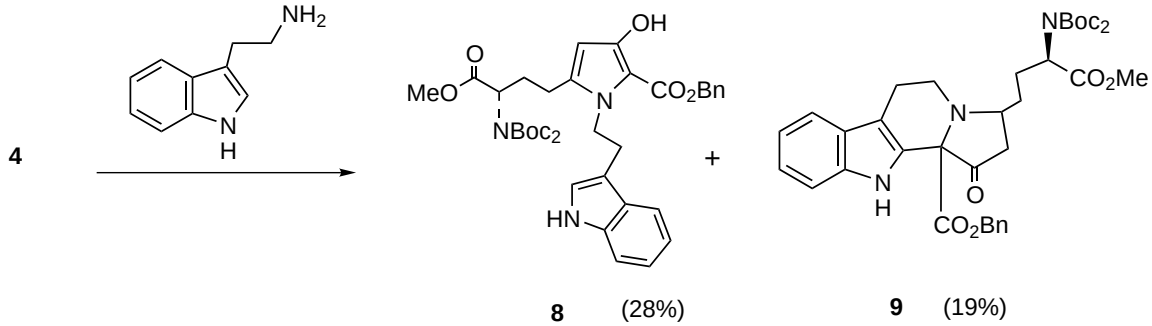
1,6-Diamino hexane underwent bis addition to the alkenyl tricarbonyl yielding the alkyl-bridged bipyrrole **7**. With tryptamine, the reaction took place through the typical pyrrole-forming route yielding **8** along with a secondary product **9** involving intramolecular addition of the indole ring to the iminium intermediate. The structural assignment to **9** was based on the ^{1}H, ^{13}C NMR and HRMS. Similar reactions were carried out using aspartic acid as the starting material.[11]

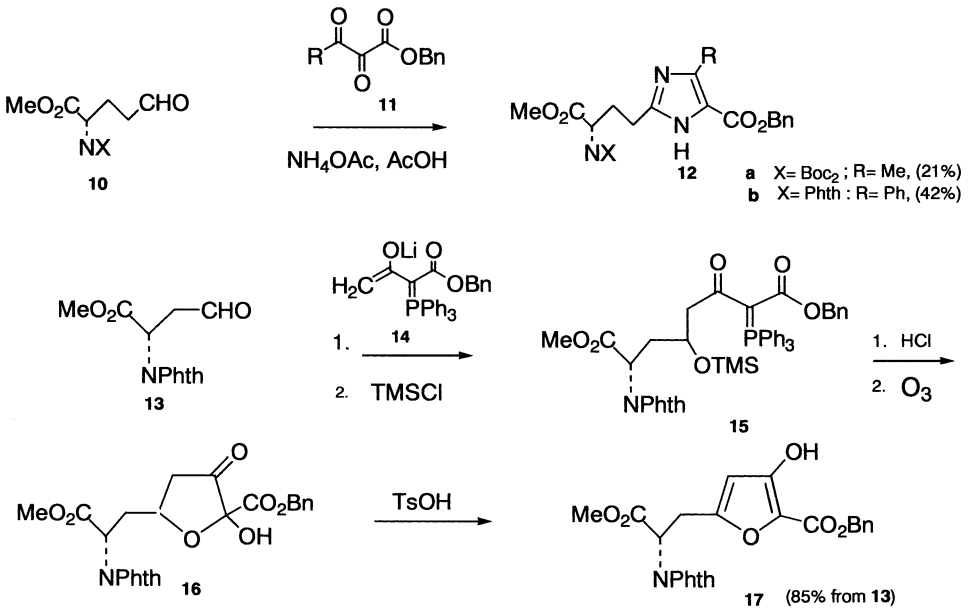
In a second phase of this work, our goal was the preparation of imidazole derivatives from the aldehydo amino acid core. The formation of imidazole carboxylic acids from the reaction of aldehydes with tricarbonyl esters in the presence of ammonium acetate was previously reported by Brackeen.[12] In the present work we allowed **10**, $X=Boc_2$ to react with the tricarbonyl ester **11**, $R=Me$ in the presence of ammonium acetate forming the imidazole carboxylate **12a**. Low yields in this transformation may have resulted from the presence of considerable enol in **11**, $R=Me$, as evidenced by the ^{1}H NMR spectrum. With a non-enolizable tricarbonyl **11**, $R=Ph$ and an aldehyde ester containing the phthalimide protecting group **10**, $X=Phth$ the imidazole product was formed in improved yield.

Based on procedures which we have previously developed,[13] this methodology could also be applied to the formation of furan derivatives of α-amino acids. Thus, the phthalimide protected aldehyde ester **13** derived from aspartic acid dibenzyl ester underwent reaction with the lithiated tricarbonyl derivative **14** in the presence of TMSCl to form the TMS protected alcohol **15**. Deprotection of the alcohol (HCl) followed by ozonolysis yielded a tricarbonyl which underwent cyclization to **16**, and then conversion to the furan **17** in the presence of TsOH.









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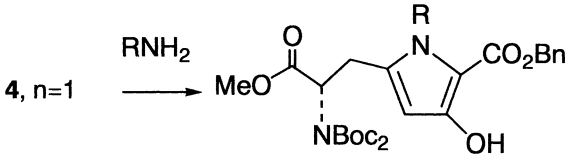
11. Reactions of the aldehydo ester derived from aspartic acid with amines yielded pyrroles as shown:



R= CH_2Ph, (72%)
R=$(CH_2)_3OH$, (68%)
R=$(CH_2)_3Br$, (75%)

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