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Tetrahedron Letters 44 (2003) 361–363

TETRAHEDRON LETTERS

α,β-Diketo nitriles as dielectrophiles. Formation of heterocyclic derivatives of amino acids

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Received 28 October 2002; revised 5 November 2002; accepted 6 November 2002

Abstract—The reactions of mono Boc-protected amino monocarboxylic acids with phosphoranylideneacetonitrile yield ylido nitriles which on ozonolysis at low temperature form labile α,β-diketo nitriles. These derivatives may be used in situ for reaction with diamines or related dinucleophiles to yield hetero derivatives of interest as unnatural amino acid building blocks.

The synthesis of unnatural amino acids is an area of research that has attracted a great deal of attention in recent years.[1,2] Some of these systems exhibit important biological properties, such as antibiotic and antitumor activity and others have been shown to serve as protease inhibitors useful in the preparation of new drug candidates. Incorporated into polypeptides, they have been used to probe enzyme structure and function or to develop new libraries for DNA binding.[3]

Synthetic methodology based upon the vicinal tricarbonyl aggregate has proven to be extremely versatile. In particular, the route which allows ready conversion of a carboxylic acid to the highly electrophilic vicinal tricarbonyl (VTC) system has made possible the generation of a varied range of heterocyclic systems[4] not readily available by conventional methods. A notable application of this chemistry has recently been reported by Baldwin who has shown that vicinal tricarbonyl esters formed from aspartic and glutamic acids may be converted to derivatives of interest as heterocycle-substituted non-proteinogenic amino acids.[5]

In our ongoing research on tricarbonyl and related compounds, we have studied the chemistry of cyano dicarbonyl analogues of VTC.[6] These electrophiles are more reactive than the corresponding tricarbonyls, and undergo unique reactions with nucleophiles in which the nitrile function behaves as a leaving group. Due to their enhanced reactivity, they are most conveniently prepared in situ at low temperature, and used without isolation as precursors to α-keto amides, esters and acids. In this report we describe application of this methodology to the formation of novel heterocyclic derivatives of α-amino acids.

We first studied the behavior of *N*-Boc 6-aminohexanoic acid (**1**) in the sequence outlined in Scheme 1. Reaction of **1** with ylido nitrile **2** gave α-keto cyanophosphorane **3** which was then subjected to ozonolysis at −78°C to form the cyano dicarbonyl product **4**. This labile electrophile was not isolated but allowed to react directly with 1,2-phenylenediamine, yielding a mixture of the substituted quinoxalines **5** and **6**.

The same reaction was then applied to the mono benzyl ester of *N*-Boc aspartic acid **7**. As outlined in Scheme 2, generation of the cyano ylide **8** was followed by ozonolysis to yield the diketo nitrile **9** which was immediately treated with 1,2-diphenylenediamine, forming the hydroxy quinoxaline **11** (96%). We suggest that this reaction takes place through the addition product **10** (X = H) followed by the elimination of HCN. When 4,5-dichloro-1,2-diphenylenediamine was used as a nucleophile, the corresponding cyano quinoxaline (**12**) was formed (71%). In this case, it appears that the electronegative chlorine substituents on the aromatic ring increase the lability of the NH hydrogen in **10**, X = Cl, favoring the competing loss of H_2O.

The above reactions yielded products substituted with either hydroxy, nitrile, or a mixture of the two. We found that selectivity could be achieved by a modification in the procedure involving the generation in situ of the α-keto ester **4a** (Scheme 1) corresponding to the α-keto nitrile **4**. Thus, in the ozonolysis of **3**, we per-

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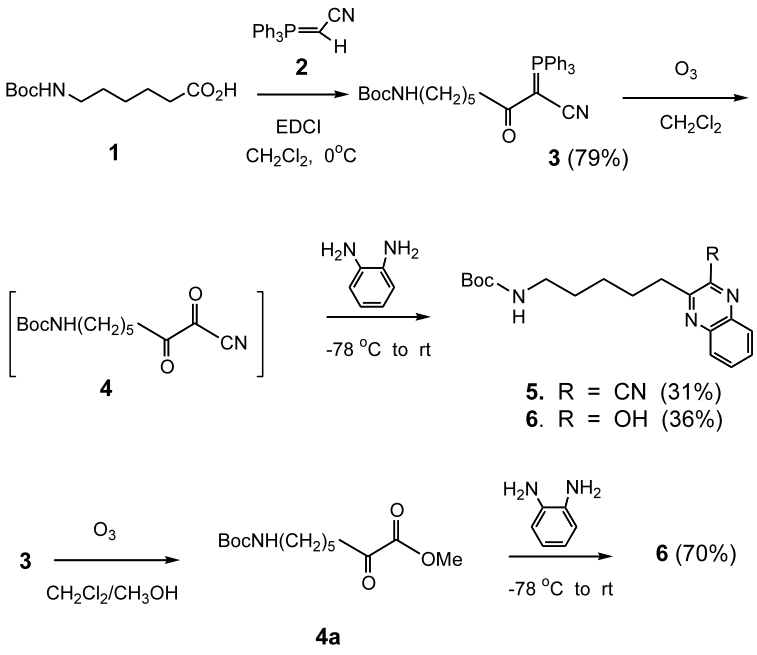
PII: S0040-4039(02)02486-3



Scheme 1.

formed the oxidative cleavage in CH_3OH/CH_2Cl_2, in which case the hydroxy substituted product **6** was formed exclusively (70%) from **4a**. In the same way, **13**, the hydroxy analog of **12** formed from **9** (Scheme 2), could also be prepared (72%) through the α-keto ester route as the only quinoxaline product.

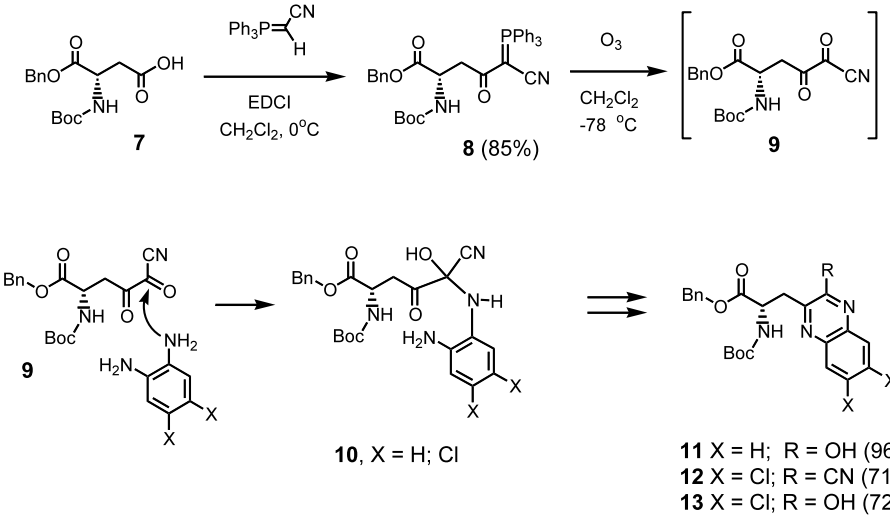
With 2-aminobenzylamine, only compound **14** was formed (64%) in both solvent systems (Scheme 3).[7,8a] Using 2,3-diaminopyridine as the dinucleophile in reaction with **9** employing CH_2Cl_2 as the solvent, we obtained the pyrido pyrazine **15** as the sole product (40%).[8b] This compound was isolated in improved yield (85%), when the ozonolysis was carried out in CH_3OH/CH_2Cl_2 yielding an α-keto ester intermediate, for the amination.

With thiourea (Scheme 3), a mixture of diastereomeric products **16** and **17** was obtained (83%) in CH_2Cl_2.

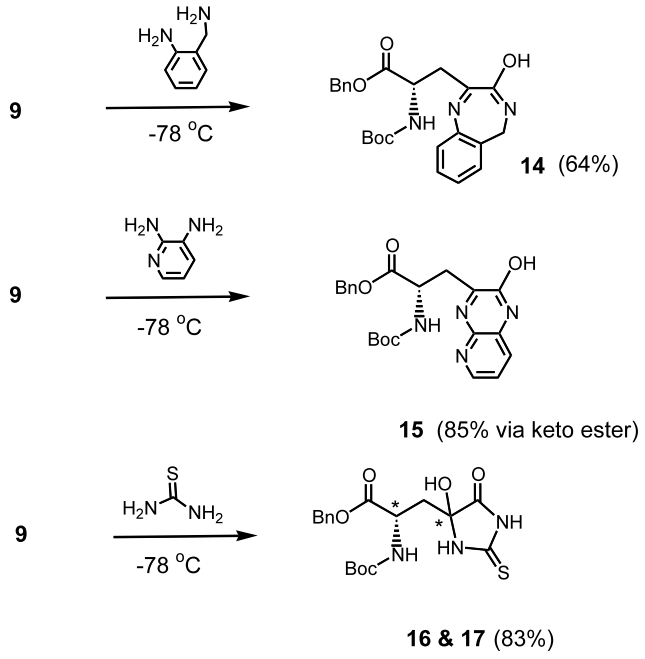
Supporting information available. ^1H, ^{13}C and HRMS spectroscopic data for all new compounds.

Acknowledgements

This work was supported by grants from the NIH and NSF. We thank Dr. Walter McMurray of the Yale



Scheme 2.



Scheme 3.

Cancer Center Mass Spectrometry Resource for help in determining HRMS spectra of new compounds prepared in this synthesis.

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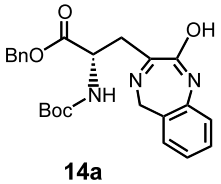
7. In CH_2Cl_2, the yield was 64%; in CH_3OH/CH_2Cl_2, the yield was 82%.
8. (a) We assign structure **14** to this addition product rather than the closely related alternative **14a** based on the expectation that the more basic primary amine would react preferentially and irreversibly with the α-keto carbonyl group in **9**;



14a

(b) In the same way, we assume that the more basic amino residue located *meta* to the ring nitrogen in 2,3-diaminopyridine would take part in an initial attack at the α-keto position of **9**.