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Synthesis of γ-*N*-acylamino-β-keto esters and ethyl 5-oxazoleacetates via Ritter reaction and hydration of γ-hydroxy-α,β-alkynoic esters☆

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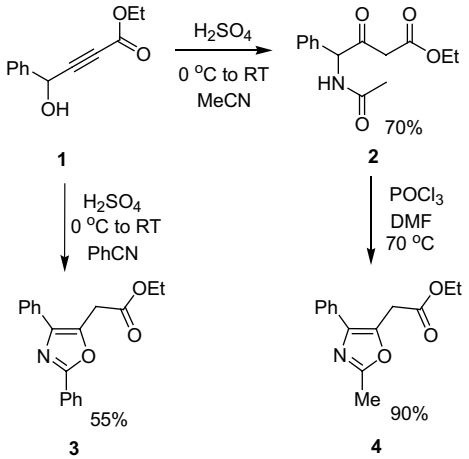
Abstract—The classical Ritter reaction on γ-hydroxy-α,β-alkynoic esters produced γ-*N*-acylamino-β-keto esters or ethyl 5-oxazoleacetates using alkyl or aryl nitriles, respectively. The γ-*N*-acylamino-β-keto esters resulting from alkyl nitriles are useful intermediates in the synthesis of a variety of building blocks. We also show that these can be converted into ethyl 5-oxazoleacetates using an additional step involving $POCl_3$.

The reactions of nitriles with relatively stable carbocations generated in situ from alcohols or alkenes generally provide amides (the Ritter reaction).[1] In connection with an ongoing project,[2] we were interested in the synthesis of γ-amino-α,β-alkynoic esters starting from the corresponding hydroxy compounds. As an obvious choice, we carried out the Ritter reaction on **1** using conc. H_2SO_4 in acetonitrile to give the corresponding γ-acylamino-α,β-alkynoic ester. However, the spectral data of the product showed it to be γ-*N*-acylamino-β-keto ester **2**. We further confirmed the structure as **2**, by converting it to the known ethyl 5-oxazoleacetate derivative **4** by heating with $POCl_3$ in DMF. The formation of compound **2** is the result of a combination of a Ritter reaction with hydration on the γ-hydroxy-α,β-alkynoic ester **1**. To our delight, the same reaction in benzonitrile produced ethyl 5-oxazoleacetate **3** in 55% yield, which resulted from an additional cyclization step (Scheme 1). Based on these initial observations, we have developed a novel method to synthesize γ-*N*-acylamino-β-keto esters and ethyl-5-oxazoleacetate derivatives starting from the corresponding γ-hydroxy-α,β-alkynoic esters.

Compounds of type **2** are equivalents of *N*-protected *C*-acylated amino acid derivatives, which are important building blocks in the synthesis of natural products, heterocycles, β-amino alcohols, and peptidomimetics.[3] The γ-*N*-acylamino-β-keto esters can only be accessed via *C*-acylation of acyl imidazoles which in turn are derived from the corresponding *N*-protected amino acids as described by Masamune and Brooks.[4] As a consequence, there is a need for the development of new and better methods to access these important compounds. Our



Scheme 1.

Keywords: Ritter; Hydration; Oxazoleacetates; γ-hydroxy-α,β-alkenoic esters.

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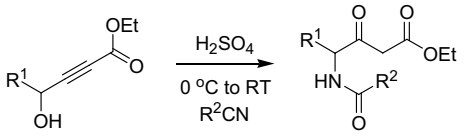
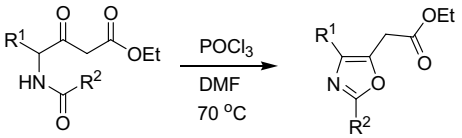


R^1	R^2	Yield	Product
C_6H_5-	$CH_3CH_2CH_2$-	66%	**5**
C_6H_5-	$C_6H_5CH_2$-	65%	**6**
4-F-C_6H_4-	CH_3-	67%	**7**
4-F-C_6H_4-	$CH_3CH_2CH_2$-	60%	**8**
2-F-C_6H_4-	CH_3-	55%	**9**
4-Me-C_6H_4-	CH_3-	64%	**10**
4-Me-C_6H_4-	$CH_3CH_2CH_2$-	63%	**11**
4-^{t}Bu-C_6H_4-	CH_3-	70%	**12**
4-^{t}Bu-C_6H_4-	$CH_3CH_2CH_2$-	78%	**13**

Scheme 2.

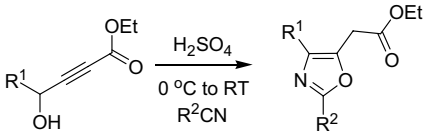
present method is efficient and operationally simple and can serve as an alternative to existing methods.

To test the generality of this method, the γ-hydroxy-α,β-alkynoic esters were readily prepared from the corresponding aldehydes by coupling with ethyl propiolate in the presence of LDA as described previously.[5] Thus, conducting the reaction on a variety of γ-hydroxy-α,β-alkynoic esters with different alkyl nitriles in the presence of conc. H_2SO_4 resulted in the corresponding γ-acylamino-β-keto esters **5**–**13**[6] in good yields.[7] This reaction failed in the case of substrates having R^1 as an alkyl group. These results reveal that only alcohols capable of giving a strongly resonance-stabilized carbocation result



R^1	R^2	Yield	Product
C_6H_5-	$CH_3CH_2CH_2$-	85%	**14**
4-F-C_6H_4-	CH_3-	86%	**15**
4-F-C_6H_4-	$CH_3CH_2CH_2$-	88%	**16**
4-Me-C_6H_4-	$CH_3CH_2CH_2$-	90%	**17**
4-^{t}Bu-C_6H_4-	CH_3-	92%	**18**
4-^{t}Bu-C_6H_4-	$CH_3CH_2CH_2$-	84%	**19**

Scheme 3.



R^1	R^2	Yield	Product
C_6H_5-	4-Me-C_6H_4-	60%	**20**
C_6H_5-	vinyl	50%	**21**
C_6H_5-	4-F-C_6H_4-	52%	**22**
4-F-C_6H_4-	C_6H_5-	58%	**23**
4-Me-C_6H_4-	C_6H_5-	62%	**24**
4-Me-C_6H_4-	vinyl	44%	**25**
4-^{t}Bu-C_6H_4-	C_6H_5-	60%	**26**
4-^{t}Bu-C_6H_4-	4-Me-C_6H_4-	70%	**27**
4-^{t}Bu-C_6H_4-	vinyl	50%	**28**

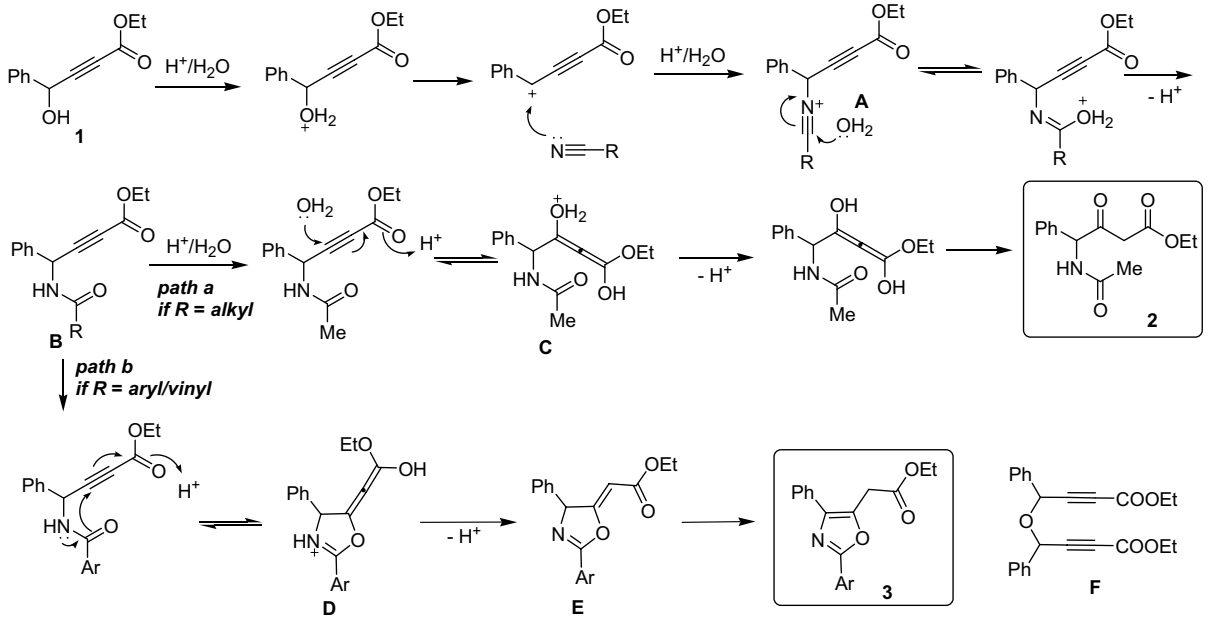
Scheme 4.

in the desired products. The results are summarized in Scheme 2.

To enhance the utility of the γ-acylamino-β-keto esters, we converted them into 5-oxazoleacetate derivatives by treatment with $POCl_3$ in DMF.[3a] Compounds containing a core 4- or 5-oxazoleacetic acid moiety show a range of pharmacological properties.[8,9] Closely related 5-oxazoleacetic acids, including 2,4-diaryl[7] and 4-aryl[7] derivatives, are capable of modulating inflammation and hyperglycemia, respectively. Taking into consideration these findings, it is important to develop new and improved methods to synthesize 5-oxazoleacetic acid derivatives. In all cases reaction with $POCl_3$ produced the desired 5-oxazoleacetates (**14**–**19**)[6] in excellent yields (Scheme 3).

The Ritter reaction on γ-hydroxy-α,β-alkynoic esters in the presence of arylnitriles or acrylonitrile furnished 5-oxazoleacetic acid derivatives in good yields (Scheme 4). Although, several synthetic procedures are available for the synthesis of oxazole derivatives, there is no straightforward method for the synthesis of 5-oxazoleacetates. Thus the present method provides an efficient route to this class of oxazole derivatives. We have generalized the method with various substrates to give products **20**–**28** in good yields (Scheme 4).[6,7] In the case of alkyl nitriles, all attempts (longer reaction times, high temperatures etc.) to synthesize oxazoleacetates in a one-pot fashion were unsuccessful.

Based upon these observations, we propose a mechanism (depicted in Scheme 5) for the conversion of γ-hydroxy-α,β-alkynoic esters into γ-acylamino-β-keto esters or 5-oxazoleacetates. According to this mechanism, initially intermediate **B** is formed from the



Scheme 5.

nitrilium ion **A** via a Ritter reaction on **1**. Intermediate **B** can follow either paths (a or b) depending on the nature of nitrile. Thus, path a is favored in the case of an alkyl nitrile where addition of a water molecule takes place across the triple bond followed by loss of a proton then tautomerization leading to the product γ-acylamino-β-keto ester **2**.[10] Path b is favored in the case of aryl nitriles in which formation of intermediate **D** through intramolecular cyclization followed by loss of a proton results in intermediate **E** (Scheme 5). When R is an aryl or a vinyl group, extended conjugation in intermediate **D** may be the driving force for the formation of 5-oxazoleacetates in a one-pot sequence. This is in line with the recent findings from Wipf's group, where they described the synthesis of oxazoles from propargyl amides using silica gel.[11] In some cases, we also observed trace amounts of the dimer **F** formation, which can be explained by the addition of another molecule of **1** on to the carbonium ion.

In conclusion, we have developed a new method for the synthesis of γ-*N*-acylamino-β-keto esters and ethyl 5-oxazoleacetates using alkyl and aryl nitriles, respectively, with a reaction protocol that is cheap, and operationally simple. The present method provides advantages over those currently available and should further enhance the utility of γ-*N*-acylamino-β-keto esters and ethyl 5-oxazoleacetates. New synthetic applications of γ-*N*-acylamino-β-keto esters to generate a variety of building blocks will be the subject of future work.

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6. All new compounds were characterized on the basis of IR, ^{1}H, ^{13}C, MS and HRMS.
7. In a typical experiment, to an ice-cold solution of γ-hydroxy-α,β-alkynoic esters in alkyl nitrile solvent, concd H_2SO_4 (2 equiv) was added carefully and the reaction stirred at room temperature for 6–10 h. After the disappearance of starting material (monitored by tlc) the reaction was quenched with aq $NaHCO_3$ solution and

work-up followed by flash column chromatography gave pure γ-acylamino-β-keto esters.

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