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Functionalizing the γ -Position of α -Diazo- β -ketoesters

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Abstract

Although α -diazo- β -ketoesters are synthetically versatile intermediates, methodology for introducing this functionality into complex molecules is still limited, most frequently involving a carboxylic acid precursor, which is then activated and transformed into a β -ketoester, with the diazo group being subsequently added with a diazo transfer reagent. While introducing this highly functional moiety in a convergent one step process would be ideal, such an objective is limited by the relatively few studies which address functionalization of the α -diazo- β -ketoester at the γ -position. In the present investigation, we evaluate strategies, both new and established, for functionalizing α -diazo- β -ketoesters, particularly with regard to generating compounds prospectively useful in the synthesis of C1-substituted carbapenems. We report the first δ -aldehydo- α -diazo- β -ketoester as well as a method for its oxidation to the corresponding methyl ester, and the formation of a new substituted pyrazole under basic conditions.

Graphical abstract

Keywords

Diazo; β -ketoester; carbapenem; pyrazole

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Supplementary Data

Supplementary data is provided detailing experimental procedures and spectroscopic information on compounds **12–20**, **23**, **25**, **26**, and **28** and crystallographic information on compound **23**. This information can be found in the online version at:

Introduction

We would like to report our recent research involving the synthesis and reactivity of γ -substituted- α -diazo- β -carbonyl compounds. Long recognized for their ability to undergo synthetically useful insertion reactions, α -diazo- β -dicarbonyl compounds are of ever increasing utility. These compounds are prepared from β -ketoesters via diazo transfer reactions¹ and are valuable intermediates in the synthesis of heterocyclic systems, notably including the synthesis of carbapenems as shown in Scheme 1.² The stabilized diazo group is capable of selective, and directed, activation with transition metals, including Rh^{II}, especially Rh₂(OAc)₄ and Rh₂(esp)₂,³ Cu^I,⁴ Cu^{II},⁵ Ru^{II},⁶ as well as Rh^{III},⁷ Ir^{III},⁸ and Co^{III},⁹ to affect a wide array of intramolecular and intermolecular insertion reactions (N-H,¹⁰ O-H,¹¹ and C-H¹²) and addition of the carbenoid to alkenes.¹³ The diazo functionality is also susceptible to strongly electrophilic reagents under non-catalytic, conditions, including reactions with bromine and dimethyldioxirane, as shown in Scheme 2.^{14,15}

In complex molecules, the α -diazo- β -ketoester functionality is often introduced in a stepwise fashion, from a functionalized carboxylic acid, which is then activated and converted to a β -ketoester, and subsequent introduction of the diazo functionality by diazo transfer, as shown in Scheme 3. It may be more synthetically efficient, however, to introduce the 4-carbon functionality in one piece, as shown in Scheme 4, but synthetic methodology for selectively attaching substituents to the γ position is limited. In view of the recently enhanced synthetic versatility of α -diazo- β -ketoesters, the efficient utilization of methodology for γ -position transformations is essential. It is also possible that efficient methodology may have broader synthetic utility. For example, it may be possible to utilize the diazo group to block reactivity at the normally more reactive α position of β -ketoesters, allowing selective reaction at the terminus of the system, subsequently utilizing the now numerous reactions of the diazo functionality to introduce new bonds at the carbon between the two carbonyl groups.

Results

With the objective of utilizing this approach in our ongoing studies involving the preparation of C1-substituted carbapenems,¹⁶ we would now like to report our assessment of available and new methodology for the synthetic manipulation of these valuable intermediates. To effect the diazo transfer reaction on *p*-nitrobenzyl acetoacetate, we were able to employ an inexpensive combination of methanesulfonyl chloride and sodium azide, in the presence of NaHCO₃, as shown below to generate methanesulfonyl azide *in situ*. After completion, *p*-nitrobenzyl α -diazo- β -ketoester **12** cleanly precipitates from the acetone/water solvent when cooling to 0 °C, thus enabling the rapid formation of this highly stabilized α -diazo- β -ketoester. We chose to explore the allylation of the terminal methyl, first through the corresponding enolate. However, after examining several bases (e.g. LDA, NaH, or KH) and allyl iodide, we were unable to achieve an acceptable yield of the corresponding allylated α -diazoketoester **13** as shown in Scheme 5.

We thus chose to explore reactions of the corresponding TBS enol ether **14** as shown below. Silyl enol ethers of α -diazo- β -ketoesters have proven to be useful synthetic intermediates in

reaction with selected electrophiles,¹⁷ and, with loss of the reactive diazo functionality, in rhodium-catalyzed enantioselective additions to enol ethers,¹⁸ in rhodium-catalyzed cycloadditions with 1,3-dienes,¹⁹ and other rhodium-catalyzed cycloadditions involving enol carbenoid intermediates.²⁰

Our objective, however, was to effect simple chain extension and/or functionalization of the α -diazo- β -ketoester while maintaining the reactive diazo functionality in the product, and we found that reaction of **14** with more potent electrophiles, including ICl, HC(OMe)₃ in the presence of ZnCl₂,^{17c} and allyl iodide in the presence of silver trifluoroacetate allowed the production of functional and chain-extended α -diazo- β -ketoesters as shown in Scheme 6.

The iodide could be further converted into numerous other substituted α -diazo- β -ketoesters, as shown in Scheme 7. Acetal **16** was deprotected to the corresponding aldehyde **20** in good yield. This is the first example of a δ -aldehydo- α -diazo- β -ketoester, and exists in equilibrium with its enol tautomers **24**. We subsequently reacted aldehyde **20** with 3-(*tert*-butyldimethylsilyloxy)ethyl-4-acetoxiazetidinone **21** as shown in Scheme 8. However, instead of producing a C1-substituted carbapenem precursor, **22**, the product was pyrazole **23**, the structure of which was crystallographically verified as shown in Figure 1.

As we again envisioned the formation and use of a stabilized γ -carbanion, we attempted oxidation of β -ketoaldehyde **20**, initially using the Pinnick oxidation. This reaction produced only the chloride **25**, the structure of which was verified by preparation directly from iodide **15** as shown in Scheme 9. This compound was presumably formed by the trapping of the enol tautomer **24** by adventitious HOCl, followed by oxidation and decarboxylation. Thus to achieve the desired oxidation, and bypass the easily decarboxylated β -ketoacid, we were able to oxidize **20** using 1 eq of oxone in methanol,²¹ to directly produce methyl ester **26** as shown in Scheme 10. This material could likewise be utilized in reaction with the acetate to produce pyrazole **28**.

Two recent publications have also observed the formation of pyrazoles from substituted α -diazo- β -dicarbonyl compounds, made using other methodology.²² Mechanistically, the reaction likely follows an electrocyclic process, similar to the more highly studied vinyl diazomethane system,²³ with the initially formed enolate rearranging to the crystallographically observed more thermodynamically stable nitrogen anion before reacting with the acyl imine as shown in Scheme 11.

In summary, we have demonstrated that the γ -position of α -diazo- β -ketoesters can be efficiently functionized through their corresponding silyl enol ethers, and we have developed a viable method for the selective oxidation of δ -aldehydo- α -diazo- β -ketoester **20**, and methodology for preparation of substituted pyrazoles. We have demonstrated that the α -diazo- β -ketoester moiety is stable to a wide array of reaction conditions, but also shown that selected functionality, particularly including α -diazo- β -ketoesters which also include a δ -carbonyl group, are susceptible to base-promoted rearrangements to substituted pyrazoles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- New and established methods for functionalizing α -diazo- β -ketoesters are evaluated
- A new protocol for appending an allyl group to these compounds is developed
- A new preparation of γ -heteroatom-substituted diazoketoesters is presented
- The first δ -aldehydo- α -diazo- β -ketoesters are prepared
- These new aldehydes undergo base-promoted rearrangement to pyrazoles

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Figure 1.
Crystal structure of **23**.

Scheme 1.
Merck carbapenem synthesis.²

Scheme 2.

Non-catalytic reactions of α -diazo- β -dicarbonyl compounds with electrophilic reagents.

Scheme 3.

Stepwise introduction of α -diazo- β -ketoester moiety.

Scheme 4.
Proposed single-step introduction of α-diazo-β-ketoester moiety.

Scheme 5.

Initial efforts to functionalize α -diazo- β -ketoesters.

Scheme 6.

Successful efforts to functionalize a C4 α -diazo- β -ketoester synthon.

Scheme 7.
Synthetic utility of γ -iodo- α -diazo- β -ketoester **15**.

Scheme 8.

Attempted utilization of **20** in the synthesis of C1 substituted carbapenems.

Scheme 10.

Successful oxidation of **20** and attempt to utilize α -diazo- β -ketodiester **26** in the synthesis of C1 substituted carbapenems.

Scheme 11.
Mechanistic rationale for observed product **23**.