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Diazoacetoacetate Enones for the Synthesis of Diverse Natural Product-like Scaffolds

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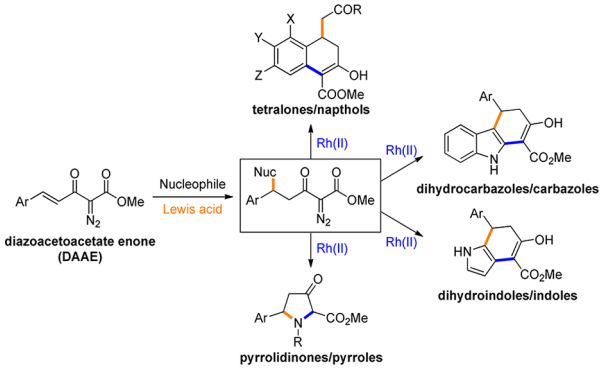
ABSTRACT



Diazoacetoacetate enones are a new class of Michael acceptors that enable the efficient construction of natural product-like scaffolds. Through their Michael addition reactions, including those with silyl enol ethers, indoles, pyrroles, and amines, δ-functionalized diazoacetoacetates are formed in high yield and with overall operational efficiency. Subsequent catalytic dinitrogen extrusion reactions provide access to a diverse series of natural product-like carbo- and heterocyclic ring systems in only three steps from commercial materials.

Complex diazoacetoacetate compounds **2** (Scheme 1) have been of particular interest in organic synthesis due to their high stability and unique reactivity relative to other classes of diazo compounds;[1] as such, they have been applied with great success in natural product total syntheses.[2] Moreover, the unique reactivity of the diazoacetoacetate functional group often compliments the conventional reactivity of comparable 1,3-dicarbonyl compounds and has resulted in the development of a variety of novel synthetic methods to construct more elaborate organodiazo compounds.[3] Most applications of the diazoacetoacetate group in targeted oriented synthesis, however, have traditionally been executed by installation of the diazo group at an advanced stage of the synthesis using an already complex carboxylic acid derivative, and reaction at the diazo functional group usually occurs in the steps immediately following its installation.[2] Recently our group has begun exploring ways to construct similarly complex diazo compounds in a more convergent way by building complexity around the readily available diazoacetoacetate subunit.[3] In an effort to broaden access to δ-substituted diazoacetoacetates **2**, whose metal-catalyzed carbene transformations provide convenient access to carbo- and heterocyclic ring systems, we devised a synthetic strategy

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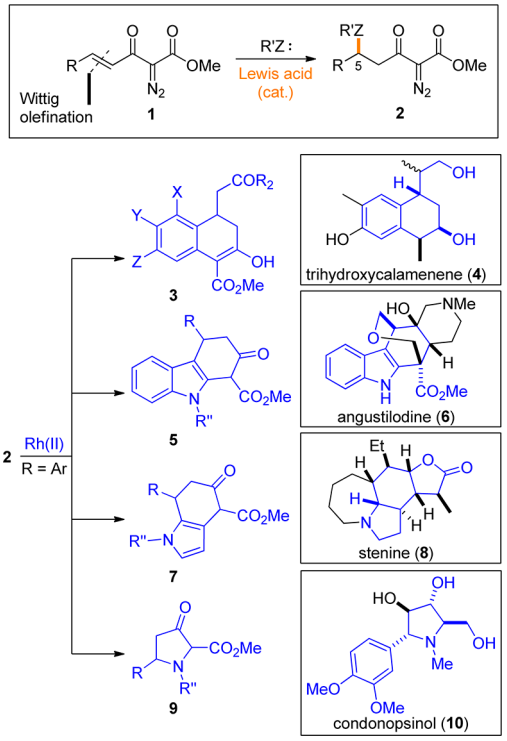
involving the general 1,4-addition of nucleophiles into diazoacetoacetate enones **1** (DAAEs, Scheme 1). In this way, the bulk of the organic framework can be conveniently installed to access **1** via a Wittig olefination reaction, and 1,4-addition reactions of a variety of nucleophiles would facilitate construction of C−C and C−N bonds at C(5) using **1** as a modular synthetic platform.

Scheme 1. Natural Product-like Scaffolds Derived from Nucleophilic Additions to Diazoacetoacetate Enones (DAAEs)



We envisioned DAAE **1** as being a general template for the construction of a variety of important, biologically relevant carbo- and heterocyclic ring systems by employing selective rhodium-catalyzed ring forming reactions on the 1,4-addition products **2** (Scheme 1). Therefore, the fate of adduct **2** in catalytic dinitrogen extrusion reactions would depend solely on the nucleophile that is chosen to functionalize **1**, since the intermediate metal carbene formed from diazo decomposition of **2** would be expected to react with the newly installed RZ functionality or the aromatic ring native to **1** (R = Ar) depending on which is more electron rich. For example, the adduct resulting from reactions with silyl enol ethers (RZ = CH_2COR'), when exposed to a rhodium catalyst, would give β-tetralone derivatives **3** by Buchner-type reactions onto the appended aromatic ring. Related tetralin natural products, exemplified by trihydroxycalamenene **4**, constitute a broad class of biologically active natural products.[4,5] On the other hand, if indoles or pyrroles are added, the electron-rich heterocycle present in **2** is expected to react preferentially to allow access to dihydrocarbazoles **5** and dihydroindoles **7**. These heterocycles are present in a variety of biologically active substances including the natural products angustilodine (**6**)[6] and stenine (**8**).[7] Finally, the reactions of **2** with amines would allow expedient access to pyrrolidinones **9** of which a large number of biologically active substances belong and in this case is exemplified by the natural product condonopsinol (**10**).[8] The proposed route to these natural product-like scaffolds represents an efficient and atom-economical approach in that both steps are catalyst controlled; except for dinitrogen, all of the atoms present in the starting materials are maintained through the sequence.

Only a few examples of diazoacetoacetate enones **1** in dinitrogen extrusion reactions have been reported;[9] however, their reactivity as electrophiles has not been explored. Since a general method for synthesizing DAAEs **1** was not available, we set out to develop a convenient one-pot protocol for the general prepartion of **1** (Table 1). Commercially available Wittig reagent **11** was chosen as the starting material,[10] and treatment of **11** with a variety of aldehydes in the presence of NaH effected olefination to provide enones that were not isolated. Rather, upon completion of the olefination reaction, buffered NEt_3 (3:1 with AcOH) and the diazo transfer agent *p*-acetamidobenzenesulfonyl azide (*p*-ABSA)[11] were added to the reaction mixture to afford DAAE **1** as mixtures (1:1 to 3:1) of (*E*) and (*Z*)-isomers. Isomerization of the (*Z*)-enones to the more thermodyamically favored (*E*)-enones was promoted by the addition of DABCO in catalytic amounts to the initial olefination reaction. This two-step/one-pot procedure cleanly provided (*E*)-diazoacetoacetate enones **1** in 64−75% yield for a series of nine different derivatives of **1** ranging in group electronegativities and subsitution.

The electrophilic behavior displayed by the library of DAAEs **1** as novel Michael acceptors (Scheme 2) was explored. Mukaiyama-Michael additions of enone **1a** with silyl enol ethers **12a**−**c** were first chosen to test the proposed electrophilic behavior of DAAE **1**. A variety of metal triflate salts was screened, and $Sc(OTf)_3$ was found to provide the highest reactivity and overall yields in CH_2Cl_2 as the solvent. For the Mukaiyama-type reactions, the use of 4 Å molecular sieves allowed these reactions to be performed in a moisture-free environment that was

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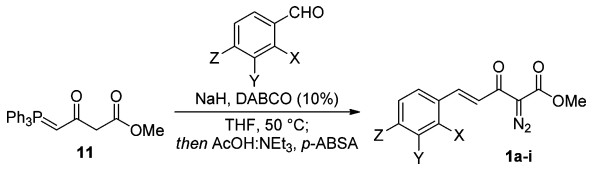
Table 1. General One-pot Synthesis of DAAEs **1**[a]



1	X	Y	Z	yield (%)[b]
a	H	H	H	65
b	H	H	OMe	67
c	H	H	Br	71
d	H	H	F	72
e	H	OMe	OMe	69
f	H	OMe	H	68
g	H	Br	H	71
h	Me	H	H	64
i	Cl	H	H	61

[a] Wittig/diazo transfer was performed reproducibly in one-pot by addition of NaH to a solution of the aldehyde and Wittig reagent on decagram scales. Upon completion of the olefination AcOH, NEt_3, and *p*-ABSA were sequentially added. Reactions were performed with the Wittig reagent as the limiting reagent; however, the aldehyde can also be the limiting reagent (see Supporting Information for procedural details). [b] Isolated yield following purification via column chromatography.

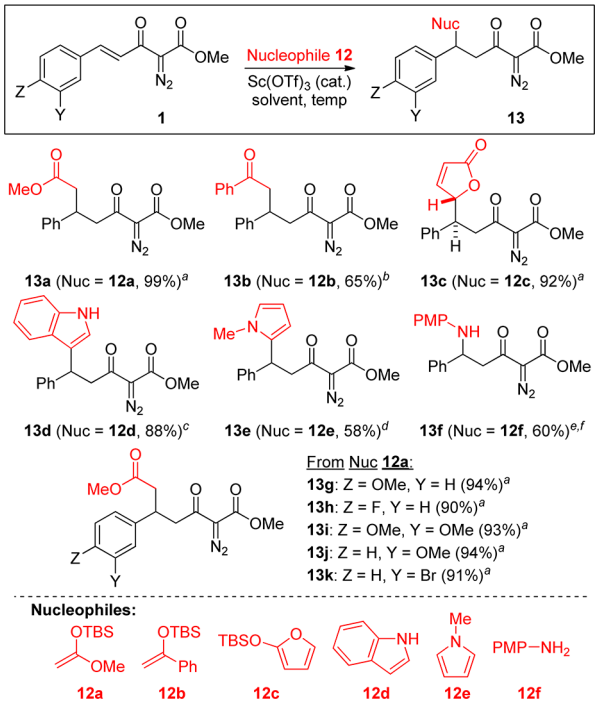
essential for high conversions. In this way, silyl ketene acetal **12a** provided carboxylate derivative **13a** in virtually quantitative yield. The use of silyl enol ether **12b** similarly gave ketone derivative **13b** in 58% yield in CH_2Cl_2; however, when this reaction was run with MeCN as the solvent with a slight increase in catalyst loading (5 mol %), the yield was improved to 65%. Lastly, siloxyfuran **12c** provided the butenolide derivative **13c** in 92% yield, and notably, the product was isolated as a single diastereomer.

The catalyst induced Friedel–Crafts-type additions of the electrophilic enone to indole (**12d**) and *N*-methylpyrrole (**12e**) were investigated as a way to prepare nitrogen containing heterocycles (Scheme 2). These reactions did not require special handling as did the Mukaiyama-type reactions; however, the use of MeCN as the solvent was crucial. Additions in CH_2Cl_2 or in refluxing toluene gave low conversions (< 50%), whereas those performed in MeCN were complete in 24 h at room temperature. The reactions of indole and *N*-methylpyrrole could also be accelerated by increasing the reaction temperature, and at 50 °C, optimal conditions provided the indole adduct **13d** and pyrrole adduct **13e** in 88 and 58% yields, respectively.[12]

Attempted addition reactions of **1a** with carbamates as amino nucleophiles did not occur, but primary benzyl amines served as good nucleophiles for this reaction. However, benzyl amine addition products were found to be prone to elimination, reverting to the starting enone **1a**, and were therefore difficult to isolate. Thus, *p*-methoxyaniline (**12f**) proved to be the ideal amino nucleophile and

(12) The addition reaction with N-methylpyrrole was accompanied by ~20% of alkylation at the C(3)-position of pyrrole.

Scheme 2. Nucleophilic Additions of Diazoacetoacetate Enones[a]



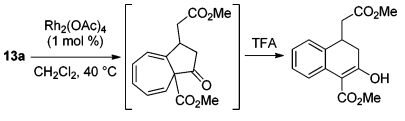
[a] Reaction performed with $Sc(OTf)_3$ (3 mol %) and 4 Å mol. sieves in CH_2Cl_2 at rt. [b] Reaction performed with $Sc(OTf)_3$ (5 mol %) in MeCN at rt. [c] Reaction performed with $Sc(OTf)_3$ (2 mol %) in MeCN at rt. [d] Reaction performed with $Sc(OTf)_3$ (5 mol %) in toluene at 50 °C. [e] Reaction performed with $Sc(OTf)_3$ (3 mol %) in CH_2Cl_2 at 40 °C. [f] PMP = *p*-methoxyphenyl.

upon reaction with **1a** under standard $Sc(OTf)_3$ catalyzed conditions afforded **13f** in 60% yield (Scheme 2).

The influence of substituents on the aromatic ring of **1** on reactivity towards 1,4-addition was assesed through reactions of silyl ketene acetal **12a** (Scheme 2). Gratifyingly, the addition reactions of silyl ketene acetal **9a** proceeded in > 90% yield regardless of the electronic nature of the aryl substitutent of **1** in the series investigated, and adducts **13g–k** were all prepared in high yields.

Having demonstrated the general reactivity of DAAE **1** as a Michael acceptor, the utility of this transformation as a template for preparing a variety of important natural product-like ring systems became the next focus (Schemes 3 and 4). Thus, Michael adducts **13a–k** were studied in diazo decomposition reactions using dirhodium(II) catalysis. Treatment of the Mukaiyama-Michael adducts **13a**,**b** and

(13) (a) The reaction of **13a** (as with **13b**,**g–k**) with $Rh_2(OAc)_4$ gave predominately the cycloheptatriene intermediate, which produced the desired tetralone upon in situ treatment with TFA:



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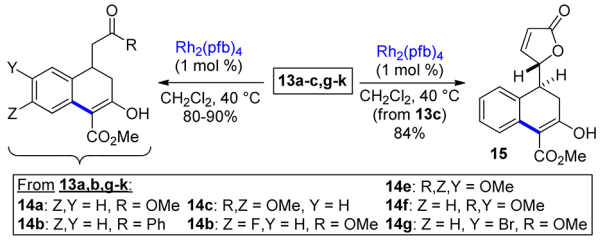
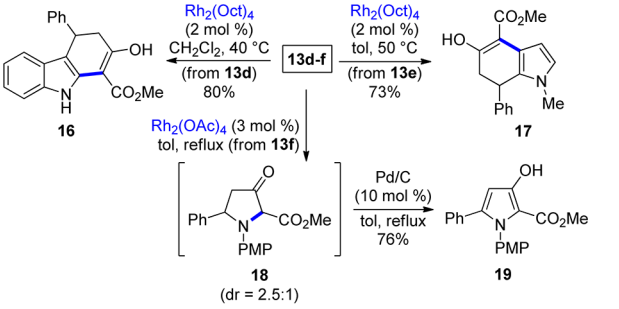
Scheme 3. Synthesis of Natural Product-like Tetralones



Scheme 4. Synthesis of Natural Product-like Heterocycles



13g–**k** with catalytic $Rh_2(pfb)_4$ in CH_2Cl_2 at 40 °C provided β-tetralones **14a**–**g** in 80–90% yield (Scheme 3). The use of $Rh_2(OAc)_4$ was effective as a catalyst; however, trifluoroacetic acid was necessary to convert the intermediate cycloheptatrienes to the thermodynamically more stable tetralones.[13] The considerably more Lewis acidic perfluorobutyrate (pfb) catalyst, however, was sufficient as a catalyst for both carbene formation and isomerization, and therefore proved superior as a catalyst. Furthermore, a series of electron-withdrawing and electron-donating groups were tolerated in both the para and meta-positions in these reactions. Another intriguing product was that produced from the reaction of butenolide **13c** with $Rh_2(pfb)_4$ (1 mol %) in hot CH_2Cl_2, which provided the tetralone-butenolide conjugate **15** as a single diastereomer in 89% yield.[14] No competitive reaction of the intermediate metal carbene with the butenolide ring was observed in this case.

The catalytic diazo decomposition reactions of heterocyclic addition products **13d**–**f** were next investigated (Scheme 4). With the indole addition product **13d**, the reaction with $Rh_2(Oct)_4$ (2 mol %) at 40 °C in CH_2Cl_2 provided the dihydrocarbazole product **16** in 75% yield. In this case $<10\%$ of the product mixture resulted from reaction of the metal carbene with the phenyl ring instead of with indole. Similarly, the reaction of the pyrrole addition product **13e** with $Rh_2(Oct)_4$ provided the intermediate dihydroindole product **17** in 73% yield. In this case, no reaction with the phenyl ring was observed. Finally, the aza-Michael product **13f** was subjected to $Rh_2(OAc)_4$ in refluxing toluene, and the reaction provided the pyrrolidinone **18** as a mixture (~2.5:1) of diastereomers. To simplify characterization, pyrrolidinone **18** was aromatized with catalytic Pd/C to afford the pyrrole product **19** in 76% overall yield.

In conclusion, we have synthesized a series of novel diazoacetoacetate enones **1**, and utilized their reactivity as general Michael acceptors with a variety of different nucleophiles to prepare a diverse library of valuable complex diazoacetoacetates **13**. Furthermore, by applying **13** in a series of selective dirhodium(II)-catalyzed ring forming reactions, we have demonstrated that the 1,4-additions of DAAEs **1** provide a versatile template for the construction of important carbocyclic and heterocyclic ring systems such as dihydroindoles, dihydrocarbazoles, β-tetralones, and pyrrolidinones.[15] As was demonstrated with pyrrolidinone **18** (Scheme 4), Pd/C catalyzed dehydrogenative aromatization reactions of **14**–**17** could similarly be used to synthesize the corresponding aromatic 5-hydroxyindoles, 2-hydroxycarbazoles, and 2-hydroxynapthols.[16] The general synthetic strategy outlined offers advantages over traditional synthetic techniques to prepare similar natural product-like ring systems because natural product-like compounds **14**–**19** can be made in only three steps from commercial materials with great functional diversity utilizing a common approach. Furthermore, the iterative metal-catalyzed steps result in an economical and environmentally friendly process due to limited regent quantities and waste generation.

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Supporting Information Available. Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for compounds **1**, **13**, and **14**–**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.