ORGANIC LETTERS

2012
Vol. 14, No. 2
440–443

Ruthenium Catalyzed Synthesis of Enaminones

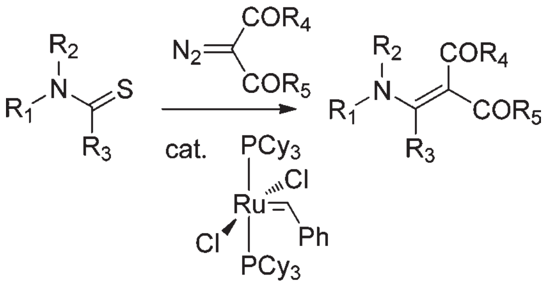
Naga Durgarao Koduri, Halee Scott, Bethany Hileman, Justin D. Cox, Michael Coffin, Lindsay Glicksberg, and Syed R. Hussaini*

*Department of Chemistry and Biochemistry, The University of Tulsa, Keplinger Hall,
800 South Tucker Drive, Tulsa, Oklahoma 74101, United States*

syed-hussaini@utulsa.edu

Received October 19, 2011

ABSTRACT



The Grubbs first-generation catalyst has been found to be an effective catalyst for the synthesis of enaminones by coupling thioamides with α-diazodicarbonyl compounds. The reaction is successful in converting primary, secondary, and tertiary thioamides into their corresponding enaminones. The reaction is also suitable for the synthesis of chiral enaminones.

Enaminones have long been used as synthetic intermediates in organic synthesis. One reason for their widespread application is their versatile reactivity, as both electrophiles and nucleophiles. Due to their value, a number of methods have been developed for the preparation of enaminones.[1]

The Eschenmoser coupling reaction provides the unambiguous formation of a particular enaminone. The reaction couples an α-halocarbonyl compound with a secondary or tertiary thioamide (Scheme 1). It is tolerant of various functional groups and base-sensitive stereocenters. As such, it has been widely used in the synthesis of natural products[2] and other bioactive compounds.[3]

However, the Eschenmoser reaction has limitations. Primary thioamides are not acceptable substrates because of their ready conversion to nitriles;[3] the reactions often require a long duration of time;[2c,4] and the coupling of secondary thioamides and α-monocarbonyl compounds is not typical. It fails to undergo sulfide contraction under mildly basic conditions and provides thioethers without the aid of additives. The reaction between piperidinethione and electron-donating monoesters does not provide enaminoesters, and instead thiazolidones are obtained.[2e,f,5] Therefore, there is a need to develop a method that can solve these issues. In this paper, we would like to report our efforts which have been successful in overcoming some of the above-mentioned restrictions.

The reactions and the applications of α-diazocarbonyl compounds in the presence of transition metals are a rapidly growing area in organic synthesis.[6] Still, the use of such

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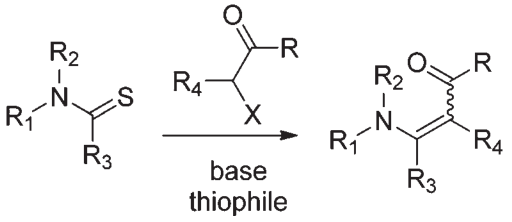
10.1021/ol202812d

Scheme 1. Eschenmoser Coupling Reaction of α-Halocarbonyl Compounds



metal carbenes, instead of halo compounds, is less known in the Eschenmoser type condensation. Copper[7] and rhodium metals have been tried in this transformation, and rhodium has been successful in producing the enaminoesters in the intramolecular reaction of *tert*-thioamides.[8] The ruthenium catalyzed condensation of α-diazocarbonyl compounds with thioamides has not previously been reported. Here, we describe the first successful use of ruthenium as the catalyst for the transformation of thioamides into enaminones.

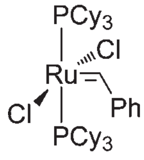
In an olefin metathesis reaction, Grubbs catalysts generate ruthenium carbenoids.[9] Since diazo compounds are generally more reactive than alkenes, we hypothesized that the formation of dicarbonyl ruthenacarbenes may also be possible by the reaction of α-diazodicarbonyl compounds with the Grubbs catalysts.[10] These dicarbonyl carbenoids are expected to be very electrophilic and highly reactive.[11] As such, like the rhodium carbenoids,[8] these ruthenium carbenoids should also be able to carry out the Eschenmoser type condensation reaction with thioamides.

To test the hypothesis, the condensation of thiolactam **1** and ethyl diazomalonate **2a** was carried out. This condensation was chosen because enaminoester **3** is one of the best yielding compounds in the Eschenmoser coupling reaction.[4b] Table 1 shows the results. The background reaction had a low yield (entry 1). Both the Grubbs first-generation **4** and Hoveyda–Grubbs second-generation **5** catalysts were successful in enacting the transformation, and using benzene as a solvent provided the best yield (entries 2–8). Also, it was discovered that the amount of catalyst could be lowered to 1.0 mol % and the equivalents of **2a** can be lowered to 1.3 without substantially compromising the yield (entries 4, 5 vs 8).

Table 1. Optimization of Ru Catalyzed Eschenmoser Type Condensation[a]

entry	2 (equiv)	catalyst	catalyst (mol %)	solvent	yield (%)
1	1.3	–	–	DCE	10[b]
2	1.3	4	1.3	CH_2Cl_2[c]	3[b]
3	2.5	5	2.0	toluene	73[d]
4	1.3	5	1.0	benzene	74[d]
5	1.3	4	1.0	benzene	73[d]
6	1.3	5	2	THF[c]	63[d]
7	1.3	5	1.7	DCE	71[d]
8	1.3	4	1.3	benzene	77[d]

[a] Reaction conditions: Heated for 26 h in a sealed tube immersed in a 120 °C oil bath. [b] Percentage conversion relative to **1** as determined by the ^1H NMR. [c] Refluxed for 26 h in a sealed tube. [d] Isolated yield.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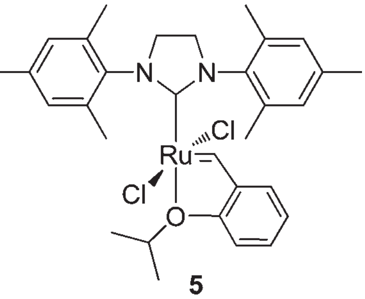
5

It was found that reproducible yields could be obtained when the reaction was performed in a pressure vessel that was heated in a 120 °C oil bath. Catalyst **5** was expected to be more stable at higher temperatures and[12] is also reported to be more suited for the generation of carbenoids with electron-withdrawing groups.[13] However, we did not observe much difference in the reactivity of **4** and **5** in this reaction (entries 4, 5). As **4** is more economical than **5**, we selected **4** for all of the subsequent transformations. The reaction generally required less time (26 h) than the reported uncatalyzed version (48 h).[4b]

In order to showcase the scope of this transformation, thioamides **6** were prepared (Table 2). Except for phenyl-(piperidine-1-yl)methanethione **6e**, all thiocarbonyl derivatives were synthesized in good yields (70–100%) by treating the respective amides with Lawesson's reagent at room temperature using CH_2Cl_2 as a solvent.[14] In addition to good yields, these conditions allow easy purification of the thiocarbonyl derivatives and only a single

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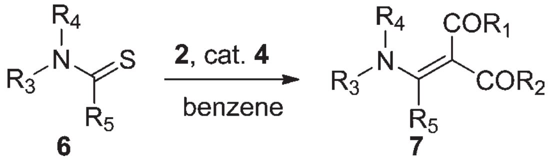
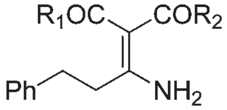
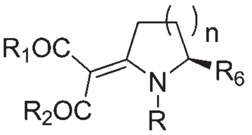
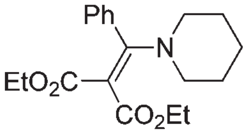
Table 2. Scope of the Ruthenium Catalyzed Synthesis of Enaminones[a]



entry	product (% yield)
	
1	**7a** $R_1 = R_2 = OEt$ (60)
2	**7b** $R_1 = Ph$, $R_2 = OEt$ (decomposition)
	
3	**7c** $n = 1$, $R = H$, $R_1 = R_2 = OMe$, $R_6 = CO_2Et$ (84)[b]
4	**7d** $n = 1$, $R = H$, $R_1 = OEt$, $R_2 = Ph$, $R_6 = CO_2Et$ (decomposition)
5	**7e** $n = 1$, $R = H$, $R_1–R_2 = OC\ (CH_3)_2O$, $R_6 = CO_2Et$ (63)
6	**7f** $n = 1$, $R = R_6 = H$, $R_1 = R_2 = OEt$ (81)
7	**7g** $n = 1$, $R = Me$, $R_1 = R_2 = OEt$, $R_6 = H$ (39)
8	**7h** $n = 1$, $R = R_6 = H$, $R_1 = OEt$, $R_2 = Me$ (47) (57)[c]
9	**7i** $n = 1$, $R = R_6 = H$, $R_1–R_2 = OC(CH_3)_2O$ (35) (45)[d]
10	**7j** $n = 1$, $R = R_6 = H$, $R_1–R_2 = CH_2C\ (CH_3)_2CH_2$ (59)[e]
11	**7k** $n = 2$, $R = R_6 = H$, $R_1 = R_2 = OEt$ (40)[b] (60)
12	**7l** $n = 2$, $R = R_6 = H$, $R_1–R_2 = CH_2C(CH_3)_2\ CH_2$ (46)[e]
13	**7m** $n = 2$, $R = H$, $R_1–R_2 = OC\ (CH_3)_2O$, $R_6 = H$ (54% relative to 6 by ^{1}H NMR)
14	 **7n** (66)
15	**7o** $R_1 = R_2 = OEt$, $R_3 = R_4 = Me$, $R_5 = CH(CH_3)_2$ (0)

[a] Reaction conditions: **2** (1.3 equiv), **4** (5 mol %), benzene, heated for 26 h in a sealed tube immersed in a 120 °C oil bath. [b] 1.3 equiv of **4** was used. [c] 2 equiv of **2** were used. [d] Heated for 36 h. [e] An equivalent of **2** was added at the beginning, after 8 and 16 h. The reaction was heated for 24 h in total.

chromatographic step was necessary for the isolation of pure thioamides.[14,15] Compound **6e** was obtained by the Willgerodt–Kindler reaction with 97% yield.[16]

The coupling of **2** with thioamides **6** was then examined. The reaction was successful for primary (entry 1), secondary (entries 3, 5, 6, and 8–13), and tertiary thioamides (entries 7 and 14) and provided low (entry 7) to high yields (entry 3) of the enaminones. However, it was necessary to use 5 mol % of the catalyst **4** to obtain consistently higher yields for all of the substrates (entry 3 vs 11). Both acyclically (entries 1 and 14) and cyclically (entries 3 and 5–13) positioned thiocarbonyl groups can be converted into enaminones. Steric hindrance was detrimental to this condensation (entries 7 and 15), as an incomplete conversion (entry 7) or no conversion (entry 15) of thioamides into enaminones was observed with increasing steric hindrance. Thioamide **6e**, substituted with a group capable of resonance contribution, was able to perform the transformation despite the steric hindrance (entry 14). This is probably due to the increased nucleophilicity of the S atom in **6e** due to the resonance contribution of the phenyl ring. The same effect can also better stabilize the reaction intermediate **14** *vide infra*.

Table 2 also shows that α-diazodiketones (entries 10 and 12), α-diazodiesters (entries 1, 3, 5–7, 9, 11, 13, and 14) and α-diazodicarbonylmonoesters (entry 8) are all viable coupling partners. In the case of unsymmetrically substituted diazo compounds, only the more stable *E* diastereomer was obtained (entry 8). The stereochemistry of the compound was determined by the ^{1}H NMR.[17] It was necessary to change the amount of diazo compounds (entries 8, 10, and 12) and the reaction times (entry 9) in certain cases to obtain reasonable yields. Still, 2-diazo-3-oxo-3-phenylpropanoate **2b** was not a suitable coupling partner under the reaction conditions and complete decomposition of the starting materials was observed (entries 2 and 4). These trends are probably due to the differences in the reactivity and the stability of the diazo compounds. In addition, dimerization of carbenoids may also be responsible for the depletion of the diazo compounds.[11d] However, no such dimerized products could be isolated in the above reactions.

Scheme 2 shows a proposed mechanism for this transformation. We speculate that α-diazocarbonyl compounds attack **4**, generating the 14 electron Ru(II) complex **12**, liberating N_2 and the enone. The additional attack of α-diazocarbonyl on **12** provides ruthenacarbene **13**.[10] Many ruthenacarbenes, including **4**, have been prepared by such a reaction of diazo compounds on **12**.[18] The nucleophilic attack of thioamide on **13** provides a metal complex-associated thiocarbonyl ylide **14** and a free ylide **15**.[6] Ylide **14** dissociates to regenerate **12** while **15** cyclizes to produce an episulfide **16**. Finally, expulsion of sulfur from **16** gives the observed eneaminones.[2a,8] The proposed species **12** is a Ru(II) complex. As such, other more economical Ru(II) sources may also be able to catalyze this reaction. Indeed,

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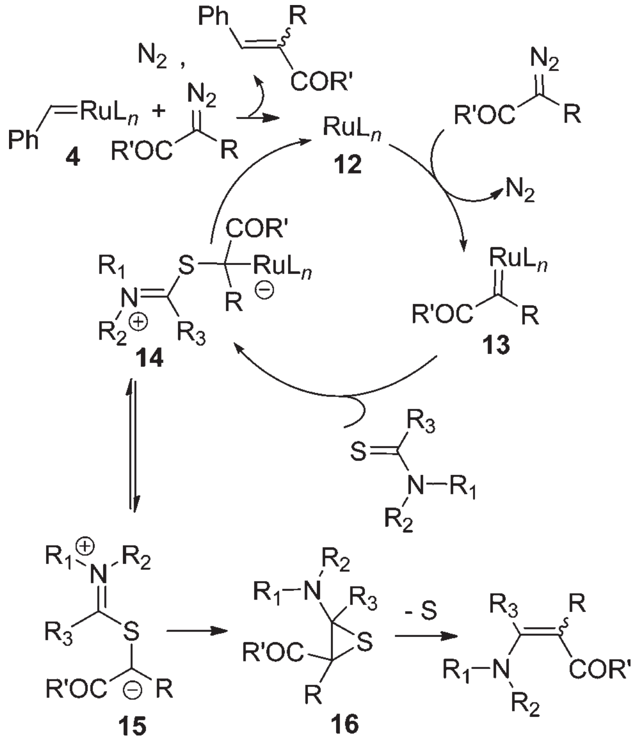
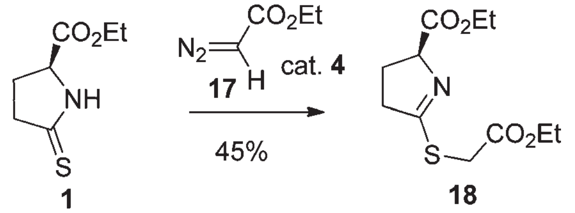
some Ru(II) complexes have been used in the generation of ruthenium carbenoids that are similar to **12**.[11b,19] We are currently investigating the feasibility of such commercially available Ru(II) complexes, and the results of the study will be disclosed in due course.

Scheme 2. Proposed Mechanism for the Ru-Catalyzed Synthesis of Enaminones



Some evidence for the proposed mechanism comes from the fact that the reaction of ethyl diazoacetate **17** with **1** produces the iminothioether **18** (Scheme 3). The reaction does not go through the episulfide contraction step (**15** → **16**) (Scheme 2) possibly because, in the case of the monoester, the anion on **15** is less stabilized as the pK_a of monoesters compared to diesters is higher.[20,4b] As such, proton transfer from the nitrogen atom of **14** or **15** takes place and **18** is obtained. In the case of α-diazocarbonyl compounds (Tables 1 and 2) no such thioether was isolated. Further work is underway to better understand the mechanism of this reaction.

Scheme 3. Thioimine Formation with Monoester Carbene[a]



[a] Reaction conditions: **17** (1.3 equiv), **4** (5 mol %), benzene, heated for 26 h in a sealed tube immersed in a 120 °C oil bath. **1** was recovered in 27% yield. Diethyl fumarate was also detected in semipure form.

In summary, we have shown that catalysts **4** and **5** can catalyze the condensation of thioamides and α-diazocarbonyl compounds. Primary, secondary, and tertiary thioamides can be converted into enaminones. Chiral and achiral, and cyclic and acyclic thioamides can undergo this reaction. Also, both catalysts **4** and **5** are more economical than $Rh_2(OAc)_4$ which has been previously used for this type of coupling reaction.[8,21] Therefore, this report is expected to broaden the scope of such condensation reactions. In addition, the carbenoid **13** and the ylide **15** proposed in the mechanism (Scheme 2) have great potential in the fields of olefin metathesis[10,11b,11c,13b,19b,19d,22] and in the chemistry of sulfur ylides respectively.[8a,23] Presently, efforts are underway to show such applications.

Acknowledgment. Financial support was provided by the University of Tulsa new faculty Lab-startup funds. H.S. and B.H., The University of Tulsa, would like to thank both the CSURP and TURC scholarship funds from the Univeristy of Tulsa. S.R.H., The University of Tulsa, is grateful for the ACS Organic Division's sponsored travel award. We thank K. P. Roberts and J. Holland, The University of Tulsa, for their help with the spectrometric measurements. This material is based upon work supported by the National Science Foundation Chemistry Research Instrumentation and Facilities program under Grant No. CHE-1048784.

Supporting Information Available. General experimental procedures and spectroscopic data for all the isolated compounds (except **1** and **2b**). This material is available free of charge via the Internet at http://pubs.acs.org.

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