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Copper-Catalyzed Synthesis of 2, 4-Disubstituted Allenoates from α-Diazoesters

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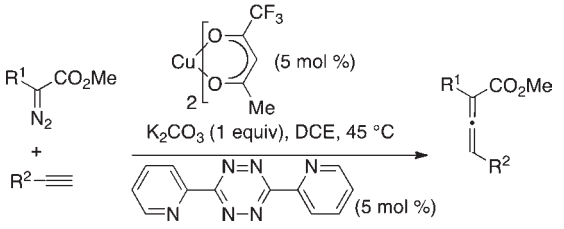
ABSTRACT



A Cu-catalyzed method for coupling α-substituted-α-diazoesters with terminal alkynes to give substituted allenoates is described. Key to the development of a selective method was the recognition that an adventitous base catalyzes the isomerization to form the allenoate product. A plausible mechanism is proposed, based in part on evidence against a mechanism that involves a Cu(I)-acetylide as a low-valent intermediate.

Allenoates are building blocks for complex molecule synthesis that have found use in a broad array of reactivities,[1] including nucleophilic addition reactions,[2] electrophilic addition reactions,[3] Morita–Baylis–Hillman reactions,[4] rearrangements,[5] and cycloaddition and formal cycloaddition reactions.[6] Of the varied ways to create allenoates,[7]

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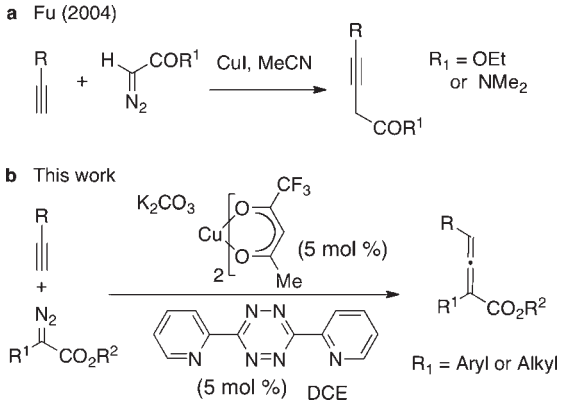
among the most versatile are methods that involve the bimolecular construction of the allene framework. Previously, such methods had generally been based on Wittig[8] or Horner–Wadsworth–Emmons reactions[9] of ketenes or ketene equivalents. Herein, we describe a complementary method for the preparation of allenoates in which the allene framework is constructed through the coupling of terminal alkynes with functionalized diazo compounds.

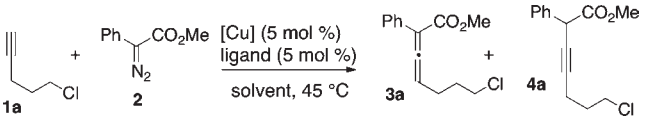
Copper complexes are known to catalyze the reaction between alkynes with alkyl diazoacetates or *N*,*N*-dimethyl-α-diazoacetamide to give 3-alkynoates and 3-alkynamides, respectively.[10] The first example of such a coupling was originally described by Jones and Deutschman,[10a] and improved catalytic systems have been described in subsequent years.[10] Most recently, Suarez and Fu described the CuI/MeCN-catalyzed coupling between alkynes with ethyl diazoacetate or *N*,*N*-dimethyl-α-diazoacetamide with high yield and efficiency to give 3-alkynoate and 3-alkynamide products, respectively (Scheme 1a).[11] In several cases, 2,3-allenoates were formed as minor products (3–5% yield) in the reactions of ethyl diazoacetate with terminal alkynes.

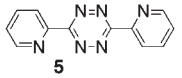
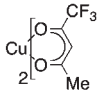
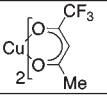
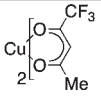
Scheme 1. Cu-Catalyzed Coupling Reactions of Alkynes with Diazo Compounds



Prior descriptions of coupling reactions between alkynes and diazo compounds have been limited to the reactivity of diazoacetates or diazoacetimides. No catalysts have been described that function in the coupling reactions of α-substituted diazoesters. Furthermore, while 3-alkynoates can be isomerized to allenoates upon treatment with base,[7b] a one-pot method for accessing 2,3-allenoates from alkynes with diazo compounds had not been described. Herein, we describe a method that couples alkynes with α-aryl-α-diazoesters or α-alkyl-α-diazoesters to provide allenoates directly in good yields (Scheme 1b).

Table 1. Selected Screening Results



entry	copper catalyst	solvent	ligand	equiv of **2**	conv of **1**	yield of **3a** + **4a**
1	CuI	MeCN	–	3	78%[b]	0%[a]
2	CuBr	DCE[c]	 **5**	3	50%[a]	38%[a]
3	$Cu(OTf)_2$	DCE	**5**	4	52%[b]	14%[b]
4	$Cu(acac)_2$	DCE	**5**	4	95%[b]	59%[b]
5		DCE	**5**	4	98%[b]	64%[a]
6		DCE	**5**	2	98%[b]	70%[a]
7		DCE	**5**	1	50%[a]	40%[a]

[a] NMR conversion or yield. [b] GC conversion or yield. [c] Inferior yields of **3a** + **4a** were obtained for analogous reactions run in toluene (<1%), MeCN (32%), THF (7%), ether (1%), or hexane (29%). Inferior yields were also obtained with bipyridine (13%), phenanthroline (10%), or 4,7-dihydroxyphenanthroline (13%).

To uncover an effective catalytic system for coupling α-substituted diazoesters with alkynes, the reaction between 5-chloro-1-pentyne (**1a**) and methyl α-phenyldiazoacetate (**2**) was studied. Selected screening results are displayed in Table 1. Most Cu(I)-catalyst systems, including CuI/CH_3CN (entry 1), did not catalyze formation of allenoate **3a** or alkynoate **4a**. However, CuBr supported by bipyridyl or phenanthroline ligands did produce these coupling products. Of the ligands and solvents studied, 3,6-di(2-pyridyl)-*s*-tetrazine (**5**) and 1,2-dichloroethane (DCE) were most effective. A number of Cu-sources were also studied, and the highest conversion and yield was obtained with Cu(II)(trifluoroacetylacetonate)$_2$. With Cu(II) (trifluoroacetylacetonate)$_2$/**5** in DCE, a 70% NMR yield of **3a** and **4a** was measured. This reaction proceeds smoothly at 45 °C: reactions at lower temperatures did not proceed to completion, and higher temperatures provided no advantage. A 2-fold excess of **2** was required; conversion of the alkyne was incomplete when only 1 equiv of the diazoester was employed.

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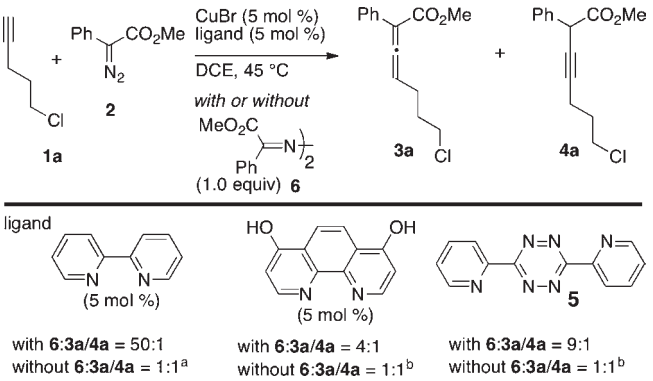
Using **5**/Cu(II)(trifluoroacetylacetonate)$_2$, we were able to obtain allenoate **3a** with high selectivity over **4a**. However, the ratios of **3a**/**4a** were inconsistent, and the selectivity was dependent on the equivalency of diazoester **2** (the selectivity increased dramatically when more than 2 equiv of diazoester **2** was used). These confusing observations prompted us to understand the factors that influence the ratio of **3a** and **4a**.

Scheme 2. Byproduct Azine **6** Improves the Ratio of **3a**/**4a**



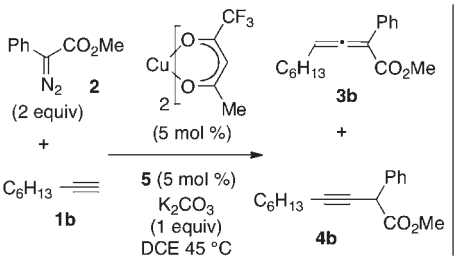
[a] 2 equiv of **2** was used. [b] 4 equiv of **2** were used.

Our efforts began with characterizing isolable byproducts from the Cu-catalyzed reactions of **1a** and **2**. One of the compounds that was isolated was the azine **6** (Scheme 2).[12] To probe the function of the azine **6**, several control experiments were run. An attempt to catalyze reaction between **1a** and **2** with **6** (5 mol %)/CuBr (5 mol %) did not lead to either of the products **3a** or **4a**. However, under conditions that typically lead to poor selectivity (CuBr/ligand combinations), the addition of azine **6** greatly improved the selectivity for **3a**. As shown in Scheme 2, the inclusion of azine **6** dramatically improved the selectivity for allenoate formation.

The observations of Scheme 2, and the inability of **6** to serve as a ligand for the coupling of **1a** and **2**, led us to hypothesize that the azine was functioning as a base that isomerizes an initially formed alkynoate to the allenoate product. Accordingly, we screened a series of simpler bases and determined that inclusion of K_2CO_3 improves the selectivity for allenoate products. Further evidence that alkynoate formation precedes allenoate formation was provided by monitoring the Cu(II) (trifluoroacetylacetonate)$_2$/**5** catalyzed reaction between 1-octyne (**1b**) and diazoester **2** (Scheme 3). The yields of products **3b** and **4b** were monitored as a function of time. After 15 min, only alkynoate **4b** (6%) is observed. After 1.5 h, **4b** is maximized (15%), but then decreases to 2% after 15 h. Concomitantly, the yield of **3b** increases from 8% after 1.5 h to 60% after 15 h.

(12) Azine dimer **6**, was independently synthesized by treating **2** with *N*-hydroxyphthalimide in the presence of rhodium(II) acetate dimer. Dimethyl 2,3-diphenylfumarate was also formed in this reaction.

Scheme 3. Time-Dependent Product Distribution[a]

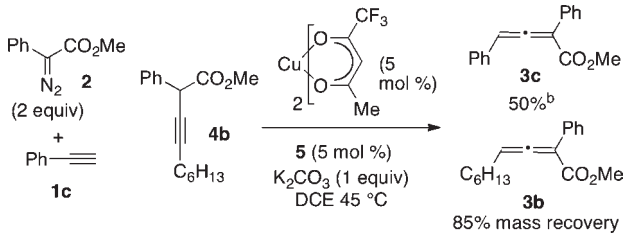


time	3b	4b
15 min	0%	6%
45 min	3%	5%
1.5 h	8%	15%
2.5 h	14%	10%
3.5 h	33%	7%
4.5 h	48%	5%
5.5 h	52%	3%
15 h	60%	2%

[a] Yields were determined by GC analysis (vs internal standard).

Finally, evidence that alkynoate products rearrange to allenoate products was obtained by including alkynoate **4b** in the Cu-catalyzed reaction between phenylacetylene (**1c**) and **2** (Scheme 4). Compound **4b** was isomerized (>95%) to **3b** with >85% mass recovery in a reaction that coupled **1c** and **2**.

Scheme 4. Alkynoate **4b**[a] Isomerizes under Coupling Conditions



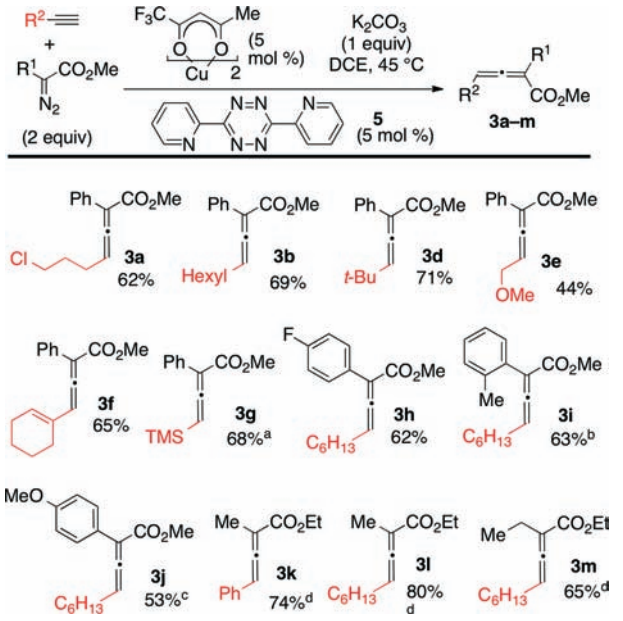
[a] Compound **4b** was added to the reaction as an inseparable 1:1 mixture with **3b**. [b] The yield of **3c** was determined by ^{1}H NMR spectroscopy, as this compound is unstable to chromatography.

The optimized reaction conditions were applied to a variety of substrates (Scheme 5). The reactions of α-aryl diazoacetates with nine aliphatic alkynes were studied and found to proceed with an average of 62% yield (44−71%). The protocol is straightforward, and syringe-pump addition of the diazoester was unnecessary. Halogen, ether, silyl, and alkene functional groups were tolerated. α-Aryl diazoacetates with aromatic substituents (*p*-F, *o*-Me, *p*-OMe) could also be utilized to give products **3h**−**j**.

Under a modified protocol, both ethyl diazopropionate and ethyl diazobutanoate were effective in this coupling reaction (Scheme 5). Because these diazo compounds were more susceptible to azine formation, a larger excess of diazoester (6 equiv) and a syringe-pump addition protocol were necessary. With these modifications, products **3k**−**m** were obtained in 65−80% yield.

With propargyl sulfides a different mode of reactivity was observed. Putative ylide formation followed by a 2, 3-sigmatropic rearrangement to give α-allenyl-α-thiophenyl esters (Doyle−Kirmse reaction[13]) was observed (see the Supporting Information). Notably, α-alkyldiazo compounds

Scheme 5. Substrate Scope for Allenoate Formation



Yields represent the average of isolated yields from two separate runs, unless noted otherwise. [a] 3:1 mixture with isomeric alkynoate **4g**. [b] Temperature was 65 °C. [c] The yield was determined by ^{1}H NMR spectroscopy, as **3j** decomposed partially upon chromatography. [d] An additional 4 equiv of diazoester was added via syringe pump. Afterward, the mixture was stirred with DBU (2 equiv) before workup.

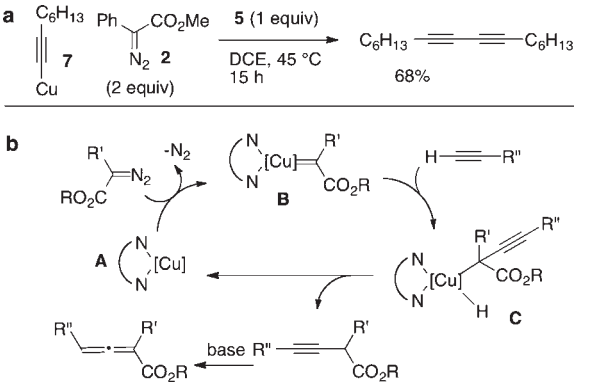
with β-hydrogens function efficiently in the transformation catalyzed by Cu(II) (trifluoroacetylacetonate)$_2$/**5**.[14] Previously, there had been few reports of using α-alkyldiazo compounds with β-hydrogens in the Doyle−Kirmse reaction,[13c,f] as such compounds can undergo an undesirable, intramolecular elimination to produce α,β-unsaturated esters.

To provide further insight into the mechanism, we also tested whether the preformed copper acetylide **7** would couple with **2** in the presence of ligand **5** (Scheme 6a). However, neither the allenoate nor alkynoate products were detected. The alkyne was converted to hexadeca-7,9-diyne, and diazoester **2** was converted into azine **6** and fumarate dimers.[12] This observation provides support for a mechanism that does not involve initial formation of a copper acetylide.

A plausible mechanism (Scheme 6b) involves the reaction of a low-valent Cu-chelate (**A**) with an α-diazoester to give carbenoid **B**. The reaction of **B** with the terminal acetylene may proceed via an intermediate **C**, which can undergo reductive elimination to regenerate **A** and the alkynoate, which isomerizes to the allenoate product.

In conclusion, a Cu-catalyzed method for coupling diazo compounds with terminal alkynes to give substituted allenoates has been developed. Key to the development of a selective method was the recognition that an adventitous base catalyzes the isomerization to form the allenoate product. A plausible mechanism is proposed on the basis of evidence against a mechanism that involves a Cu(I)-acetylide as a low valent intermediate.

Scheme 6. (a) Cu-Acetylide **7** Does Not Couple with **2**. (b) Possible Catalytic Cycle



Acknowledgment. We thank the NIGMS (NIH R01 GM068650) for financial support. NMR spectra were from instruments supported by NSF CRIF:MU, CHE 0840401.

Supporting Information Available. Full experimental details and ^{1}H and ^{13}C NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) With phenyl propargyl sulfide, ethyl α-diazopropionate gave ethyl α-allenyl-α-(phenylthio)propionate (85%), ethyl α-diazobutyrate gave ethyl α-allenyl-α-(phenylthio)butyrate (95%), and methyl α-diazo-α-phenylacetate gave methyl α-allenyl-α-(phenyl)propionate (77%).