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Copper-Mediated Aerobic Synthesis of 3-Azabicyclo[3.1.0]hex-2-enes and 4-Carbonylpyrroles from *N*-Allyl/Propargyl Enamine Carboxylates

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Supporting Information

ABSTRACT: Synthetic methods for 3-azabicyclo[3.1.0]hex-2-enes and 4-carbonylpyrroles have been developed that use copper-mediated/catalyzed reactions of *N*-allyl/propargyl enamine carboxylates under an O_2 atmosphere and involve intramolecular cyclopropanation and carbooxygenation, respectively. These methodologies take advantage of orthogonal modes of chemical reactivity of readily available *N*-allyl/propargyl enamine carboxylates; the complementary pathways can be accessed by slight modification of the reaction conditions.

Nitrogen-containing heterocycles (azaheterocycles) are an iconic component of numerous natural products, potent pharmaceutical drugs, and synthons for material-based applications. Although diverse approaches to azaheterocycle synthesis have been developed,[1] there remains a demand for versatile methodologies to construct azaheterocycles with selective control of substitution patterns from readily accessible building blocks. Herein we report a copper-mediated/catalyzed aerobic synthesis of 3-azabicyclo[3.1.0]hex-2-enes and 4-carbonylpyrroles from readily available *N*-allyl/propargyl enamine carboxylates through cyclopropanation and carbooxygenation, respectively. The different modes of reactivity may be accessed by slight modification of the reaction conditions (see Scheme 1 for examples using an *N*-allyl enamine carboxylate).

During the course of our research program on copper-catalyzed aerobic oxygenation/oxidation reactions,[2] we became interested in the potential chemical reactivity of *N*-alkenyl/alkynyl enamine carboxylates, which are easily prepared by acid-mediated condensation of the corresponding amines with β-keto esters or by conjugate addition of the amines to acetylene carboxylates.[3] Aerobic oxidative functionalization of the pendant unsaturated bonds could be envisioned to occur through the formation of a putative copper−azaenolate species.[4]

Our investigation commenced with copper-mediated aerobic reactions of ethyl 3-allylamino-3-phenylacrylate (**1a**) (Table 1). To our surprise, when **1a** was treated with 3 equiv of CuBr·SMe_2 in DMSO at 60 °C under an O_2 atmosphere, an intramolecular cyclopropanation product, ethyl 2-phenyl-3-azabicyclo[3.1.0]hex-2-ene-1-carboxylate (**2a**) was isolated in 67% yield (entry 1). While the 3-azabicyclo[3.1.0] scaffold is found in the basic core of several biologically active natural products[5] and drug candidates,[6] synthetic methods to construct this framework have been limited.[7−9] The unprecedented formation of 3-azabicyclo[3.1.0]hex-2-ene **2a** via a mechanistically intriguing cyclopropanation reaction[10] drove us to optimize the reaction conditions further. The yield of product **2a** was improved by the addition of amines

Scheme 1. Synthesis of 3-Azabicyclo[3.1.0]hex-2-enes and 4-Formylpyrroles from *N*-Allyl Enamine Carboxylates

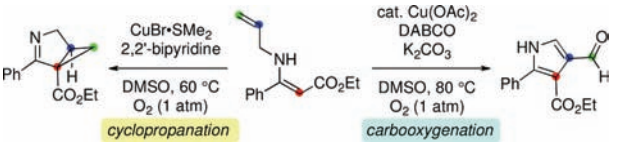
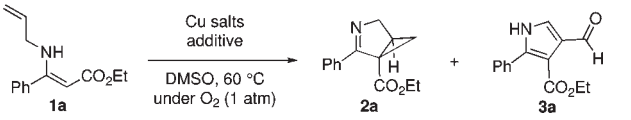


Table 1. Optimization of the Reaction Conditions[a]



entry	Cu salt (equiv)	additive (equiv)	time (h)	% yield[b,c] 2a	3a
1	CuBr·SMe_2 (3)	–	1.5	67	0
2	CuBr·SMe_2 (2.1)	DABCO (2 0)	0.7	(50)	0
3	CuBr·SMe_2 (2.1)	DMAP (2 0)	1.5	83	0
4	CuBr·SMe_2 (2.1)	1,10-phenanthroline (2.1)	1.5	88	0
5	CuBr·SMe_2 (2.1)	2,2′-bipyridine (2.0)	1.5	93	0
6	CuBr·SMe_2 (1.1)	2,2′-bipyridine (1.1)	3	89	0
7[d]	CuBr·SMe_2 (1.1)	2,2′-bipyridine (1.1)	12	(10)[e]	0
8	CuCl (1.1)	2,2′-bipyridine (1.1)	25	(67)	0
9	$CuBr_2$ (1.1)	2,2′-bipyridine (1.1)	12	0	0
10	$Cu(OAc)_2$ (1.1)	2,2′-bipyridine (1.1)	12	0	0
11	CuBr·SMe_2 (0.5)	2,2′-bipyridine (0.5)	3	(61)	(4)
12	CuBr·SMe_2 (0.2)	2,2′-bipyridine (2.0)	48	(17)[f]	(3)
13	CuBr·SMe_2 (0.2)	DMAP (3.0)	7	(34)	(6)
14	CuBr·SMe_2 (0.2)	DABCO (5.0)	2	44	(12)

[a] All of the reactions were carried out using 0.5 mmol of *N*-allyl enamine carboxylate **1a** in DMSO at 60 °C under an O_2 atmosphere. [b] Isolated yields. [c] ^{1}H NMR yields are shown in parentheses. [d] The reaction was carried out under an Ar atmopshere. [e] **1a** was recovered in 75% yield. [f] **1a** was recovered in 40% yield.

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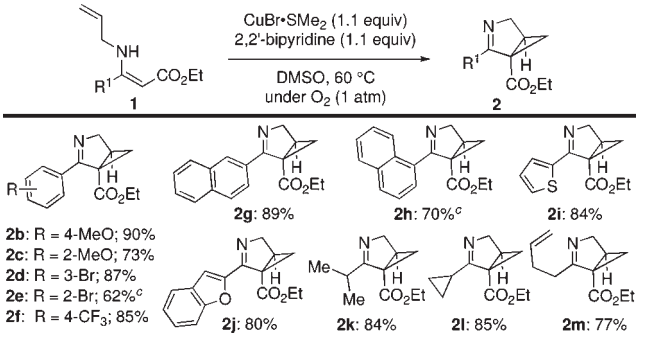
Chart 1. Scope of the Synthesis of 3-Azabicyclo[3.1.0] hex-2-enes: Substituents on the Alkene[a,b]



[a]All of the reactions were carried out using 0.5 mmol of *N*-allyl enamine carboxylate **1** with 1.1 equiv of CuBr·SMe_2 and 1.1 equiv of 2,2′-bipyridine in DMSO at 60 °C under an O_2 atmosphere for 2−3.5 h. [b]Isolated yields are reported. [c]The reaction was run using 1.1 equiv of CuBr·SMe_2 and 1.1 equiv of DMAP.

(2 equiv) to CuBr·SMe_2 (2.1 equiv) (entries 2−5); these additives may work as ligands for copper salts. The highest yield of **2a** was achieved using 2,2′-bipyridine (93% yield; entry 5). Utilization of 1.1 equiv of CuBr·SMe_2 with 1.1 equiv of 2,2′-bipyridine resulted in comparable yield of **2a** (entry 6). Under an Ar atmosphere, the reaction was sluggish and provided **2a** in 10% yield along with 75% yield recovery of **1a** after 12 h (entry 7). Although CuCl exhibited selective formation of **2a** (entry 8), Cu(II) complexes such as $CuBr_2$ and $Cu(OAc)_2$ failed to provide any **2a** (entries 9 and 10).[11] Attempts to render this process catalytic gave unsatisfactory results (entries 11−14). Under these conditions, the highest yield of **2a** (44%) was obtained using 20 mol % CuBr·SMe_2 with 5 equiv of DABCO (entry 14). In these cases, 4-formylpyrrole **3a** was formed as a minor product via carbooxygenation of the alkene.

Using the CuBr·SMe_2−2,2′-bipyridine system (Table 1, entry 6), we examined the generality of the synthesis of substituted 3-azabicyclo[3.1.0]hex-2-enes **2**. Varying the substituent R^1 of *N*-allyl enamines **1** (Chart 1) showed that benzene rings bearing either an electron-donating group (MeO in **2b** and **2c**) or an electron-withdrawing group (CF_3 in **2f**) were tolerated and that the C−Br bond remained intact when a bromine substituent (**2d** and **2e**) was introduced. 3-Azabicyclo[3.1.0]hexenes **1** bearing naphthyl (**2g** and **2h**), thienyl (**2i**), and benzofuranyl (**2j**) groups as well as alkyl groups (**2k**−**m**) were all formed in good yields. Interestingly, the reaction of *N*-allyl enamine **1m** bearing an additional pendant alkene as R^1 revealed that the cyclization reaction exclusively selects the alkene tethered to the nitrogen atom, furnishing 3-azabicyclo[3.1.0]hex-2-ene **2m** in 77% yield.

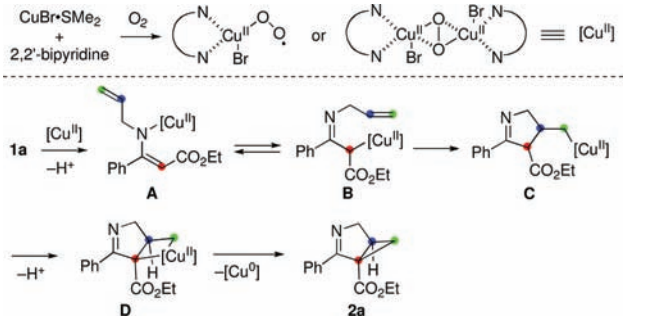
Next, the effect of the substituent on the allyl moiety in the synthesis of 3-azabicyclo[3.1.0]hexenes **2** was examined (Table 2). The reactions of both (*Z*)- and (*E*)-*N*-3-phenylallyl derivatives **1n** provided nearly 1:1 mixtures of **2n**[12] and **2n′** in good combined yields (entry 1), suggesting that the present cyclopropanation proceeds in a stepwise manner. The reaction of *N*-3,3-dimethylallyl enamine **1o** under the standard reaction conditions afforded the corresponding azabicyclo[3.1.0]hexene **2o** in 36% yield along with bromomethyl dihydropyrrole **4o-Br** (X = Br) in 13% yield. Using CuCl as the copper source with 2,2′-bipyridine provided **2o** and **4o-Cl** (X = Cl) in 58 and 23% yield, respectively. Using DMAP as the additive improved the yield of

Table 2. Scope of the Synthesis of 3-Azabicyclo[3.1.0] hex-2-enes: Substituents on the Allyl Group[a]

entry	enamines **1**	products[b]
1	***Z*-1n** ***E*-1n**	**2n** + **2n′** 60%[c] (**2n**:**2n′** = 55:45) 68% (**2n**:**2n′** = 50:50)
2	**1o**	**2o**: 36% **2o**: 58% **2o**: 63% **4o-Br**: 13%[c] (X = Br) **4o-Cl**: 23% (X = Cl)[d] **4o-Br**: < 5% (X = Br)[e]
3	**1p**	**2p**: 43% **5p**: 25%
4	**1q**	**2q-*α***: 77% **2q-*β***: 5%
5	**1r**	**2r**: 56%
6	**1s**	**2s**: 65%

[a] All of the reactions were carried out using 0.5 mmol of *N*-allyl enamine carboxylate **1** with 1.1 equiv of CuBr·SMe_2 and 1.1 equiv of 2,2′-bipyridine in DMSO at 60 °C under an O_2 atmosphere for 1.5−4 h. [b] Isolated yields are reported. [c] ^{1}H NMR yield. [d] The reaction was run using 2.1 equiv of CuCl and 1.1 equiv of 2,2′-bipyridine. [e] The reaction was run using 1.1 equiv of CuBr·SMe_2 and 1.1 equiv of DMAP.

Scheme 2. Proposed Reaction Pathway for the Formation of 3-Azabicyclo[3.1.0]hexenes



2o to 63% yield and suppressed the formation of **4o-Br** to <5% (entry 2). Subjecting chloromethyl dihydropyrrole **4o-Cl** to the standard reaction conditions resulted in a sluggish reaction that generated a complex mixture of products (see the Supporting Information). This indicates that halomethyl dihydropyrroles **4o** likely are not involved in the second C−C bond-forming step of the cyclopropanation. In the case of 2-phenylallyl enamine **1p**, 3-azabicyclo[3.1.0]hexene **2p** and trisubstituted pyridine **5p** were formed in 43 and 25% yield, respectively (entry 3). Diastereoselective

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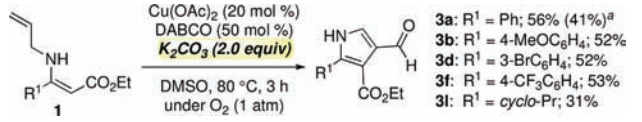
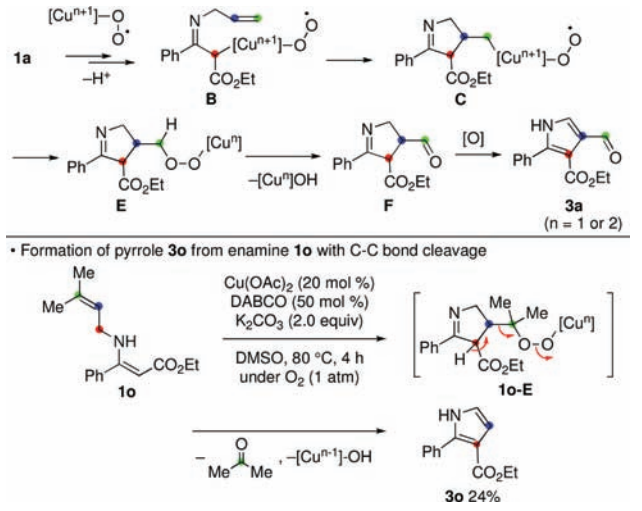
Scheme 3. Selective Formation of 4-Formylpyrroles



Scheme 4. Proposed Reaction Pathway for the Formation 4-Formylpyrroles



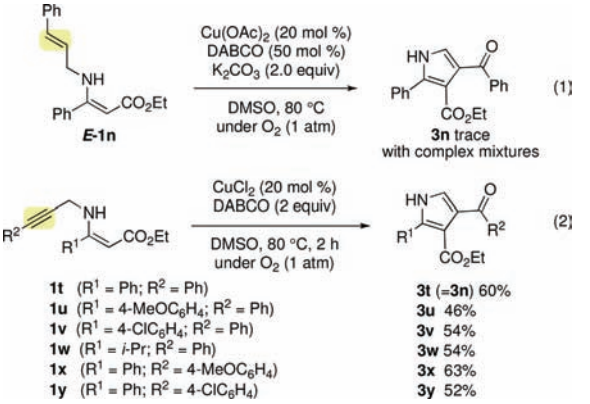
cyclization was observed from 1-phenylallyl enamine **1q**, affording α- and β-phenyl **2q**[12] in 77 and 5% yield, respectively (entry 4). The further potential of this method was probed by the reactions of cyclic *N*-allyl enamines **1r** and **1s**, which delivered highly strained fused tricyclic compounds (entries 5 and 6).

On the basis of these results, a mechanistic proposal is outlined in Scheme 2. In this senario, $Cu^{I}Br$ reacts first with molecular oxygen to form a Cu^{II} peroxo species in either monomeric or dimeric form.[13] The reaction of *N*-allyl enamine **1a** with the resulting Cu^{II} peroxo species forms copper azaenolates (**A** and **B**), which may then undergo intramolecular carbocupration of the tethered alkene moiety to generate organocopper intermediate **C**. Presumably, formation of metallacyclobutane **D** followed by a C−C bond-forming reductive elimination[14] would complete the cyclopropanation to deliver 3-azabicyclo[3.1.0]hexene **2a**. This process would allow the construction of sterically congested and highly strained molecules (e.g., **2o**, **2r**, and **2s**).

Futher exploration into reaction optimization revealed that 4-formylpyrroles **3** could be generated selectively over 3-azabicyclo [3.1.0]hex-2-enes **2** simply by adding K_2CO_3 (Scheme 3). In this case, ethyl 4-formyl-2-phenylpyrrole-3-carboxylate (**3a**)[12] was formed as a single product from *N*-allyl enamine **1a** with both Cu(I) and Cu(II) complexes.[15] The best result (56% yield) was obtained using $Cu(OAc)_2$ (20 mol %) with 50 mol % DABCO and 2 equiv of K_2CO_3. Conversely, using $CuBr\cdot SMe_2$ (20 mol %) with 20 mol % DABCO and 2 equiv of K_2CO_3 lowered the yield of **3a** to 41%. Several 2-aryl-4-formylpyrroles could be synthesized in yields of 52−56%, while the yield of 2-cyclopropyl-4-formylpyrrole **3l** was moderate (31%).

Although the role of K_2CO_3 in influencing the product selectivity remains uncertain, we propose in Scheme 4 one possible reaction pathway for the 4-formylpyrrole formation. After formation of organocopper peroxide intermediate **C** (see Scheme 2 for details), subsequent isomerization gives peroxide **E**. Elimination of $[Cu^{n}-OH]$ then affords dihydropyrrole **F** bearing the formyl group.[2,16] Further oxidation establishes aromatic pyrrole **3a**. Interestingly, the reaction of *N*-3,3-dimethylallyl enamine **1o** provided ethyl 2-phenylpyrrole-3-carboxylate (**3o**) in 24% yield via cleavage of the particular C−C bond between the carbons marked in blue and green. This result suggests the presence of a peroxide intermediate such as **1o-E**, which undergoes fragmentation to give **3o** along with elimination of acetone and $[Cu^{n-1}-OH]$.

Scheme 5. Synthesis of 4-Benzoylpyrroles



This carbonylative pyrrole formation, however, could not be applied to the synthesis of 4-benzoylpyrrole **3n** from *N*-3-phenylallyl enamine (*E*)-**1n** under the present conditions, producing instead a complex mixture of products (eq 1 in Scheme 5). It was found that the use of *N*-3-phenylpropargyl enamines **1t** in place of *N*-allyl enamines overcame this drawback (eq 2 in Scheme 5). Treatment of **1t** with 20 mol % CuCl and 2 equiv of DABCO in DMSO at 80 °C under an O_2 atmosphere gave 4-benzoylpyrrole **3t** (the same as pyrrole **3n**) in 60% yield.[17,18] The reactions of several *N*-propargyl enamines **1u**−**y** afforded the corresponding 3-benzoylpyrroles **3u**−**y** in good to moderate yields.

In summary, intriguing chemical reactivities of *N*-allyl/propargyl enamine carboxylates have been exploited to synthesize 3-azabicyclo[3.1.0]hex-2-enes and 4-carbonylpyrroles under Cu-mediated/catalyzed aerobic oxidation conditions. Slight modification of the reaction conditions allowed for a complete reversal of product selectivity. Further investigation of the scope, detailed mechanisms, and synthetic applications of the present processes to other types of molecules is currently underway.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization of all new compounds, complete ref 6a, NMR spectra, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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