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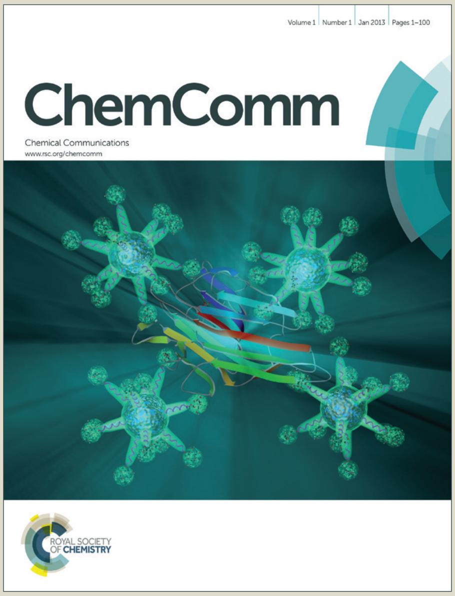

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COMMUNICATION

Aerobic Copper-Catalyzed Oxidative [6C+1C] Annulation: An Efficient Route to Seven-Membered Carbocycles†

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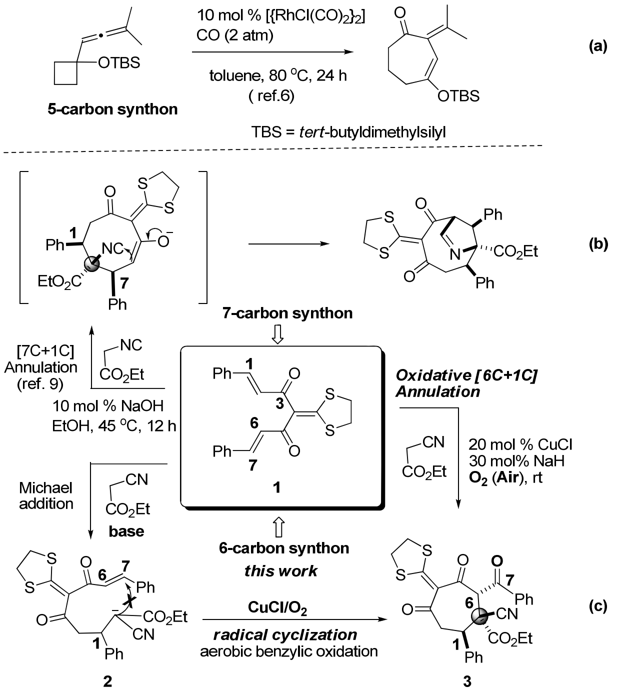
It has been revealed for the first time that co-promoted by CuCl and NaH in the presence of molecular oxygen (air), the reaction of dicinnamoyl ketene dithioacetals as the acyclic C_6 synthons with ethyl cyanoacetate gives functionalized seven-membered carbocycles. A mechanism is proposed involving a tandem Michael addition/intramolecular radical cyclization/benzyl $C(sp^3)$ –H bond oxidation.

Seven-membered carbocycles, as an important structural motif in bioactive molecules,[1,2] has received increasing interest for their construction. In this regard, the cycloadditions involving [4+3],[1a,1b,2] [5+2],[1,3] [3+2+2],[4] [4+2+1],[5a] [2+2+2+1],[5b] [3+3+1],[5c] and the formal [6+1] cycloaddition of allenylcyclobutanes as the 5-carbon synthon with CO through Rh^I-catalyzed carbonylative ring-expansion process (Scheme 1a)[6] have been realized. Although in principle there are three main approaches to construct a seven-membered carbocycle: [4C+3C],[1a,1b,2] [5C+2C][1,3] and [6C+1C] cycloaddition reaction, there is no example of the last approach (using acyclic 6-carbon synthons).[1-6]

As part of our studies on the applications of ketene dithioacetals as versatile synthons in organic synthesis,[7] the reactions involving [5C+1C][8] and [7C+1C][9] annulations have been developed. In the latter case, ethyl isocyanoacetate can serve as a Michael donor, adding to the 1,7-positions of the 1,7-dielectrophilic dicinnamoyl ketene dithioacetals **1** catalyzed by NaOH in the solvent of EtOH (Scheme 1b).[9] However, under identical reaction conditions, expansion of the [7+1] annulation methodology using ethyl cyanoacetate in place of ethyl isocyanoacetate as the Michael donor failed to give the desired [7+1] annulation product (Table 1, entry 1).

Until now, the direct synthesis of seven-membered carbocycles from acyclic precursors remains a challenge owing to entropy losses upon cyclization and no precedent for the [6C+1C] annulation reaction starting from acyclic C_6 precursors has been reported,[1–6,9] Here, we describe that, catalyzed by CuCl,[10] the seven-membered ring compounds **3**, with an all carbon quaternary centre,[11] can be constructed *via* the diastereoselective *aerobic oxidative [6+1] annulation* reaction of the readily available dicinnamoyl ketene dithioacetals **1**, ethyl cyanoacetate and molecular oxygen (from air) as oxidant under extremely mild reaction conditions in an atom-economic manner in a single step. Also needing to be figured out is that, in the [6+1] annulation process, the classical acyclic C_7 1,7-dielectrophiles can serve as the acyclic C_6 synthons (Scheme 1c).

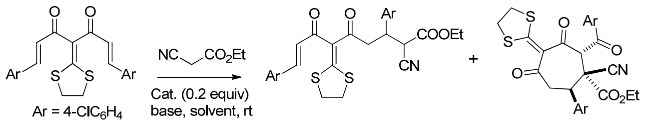


Scheme 1 [6+1] and [7+1] annulation reactions.

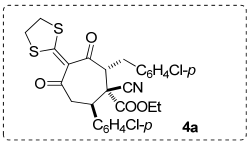
In the present research, initially, the reaction of dicinnamoyl ketene dithioacetal **1a**, (1*E*,6*E*)-1,7-bis(4-chlorophenyl)-4-(1,3-dithiolan-2-ylidene)hepta-1,6-diene-3,5-dione (prepared by the condensation of 3-(1,3-dithiolan-2-ylidene)pentane-2,4-dione with 4-chlorobenzaldehyde), (223 mg, 0.5 mmol) with ethyl cyanoacetate (1.2 equiv) was investigated as the model reaction to evaluate the possibility of the [7+1] annulation[9] using **1a** as the C_7 1,7-dielectrophile. In this case, however, **1a** was recovered in nearly the stoichiometric amount under similar reaction conditions for the [7+1] annulation of **1a** with ethyl isocyanoacetate reported previously (Table 1, entry 1).[9] It was found that, promoted by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in anhydrous DMF at room temperature in ambient air,[8c] the mono-Michael adduct **2a** was produced dominantly (entry 2). Interestingly, under similar conditions, but with the addition of catalytic amount of CuCl,[10] the reaction of **1a** with ethyl cyanoacetate gave the seven-membered instead of eight-membered ring product, cycloheptane-1,3-dione derivative **3a**, in high yield and diasteroselectivity (entry 3).

Further optimization of reaction conditions to gain the oxidative [6+1] product **3a** showed that CuCl is a better catalyst than $CuCl_2$ (entry 4 and 5) and $CuBr_2$ (entry 6) according to the yields of **3a**, DBU loading and/or reaction time required. After careful optimization of reaction conditions, product **3a** was obtained in 85% yield by performing the reaction of **1a** with ethyl cyanoacetate co-promoted by CuCl and NaH in the solvent, DMF, at room temperature in ambient air (entry 12). It should be mentioned, neither the corresponding [7+1] nor [6+1] annulation product (for example, **4a**) could be observed from the reaction of dicinnamoyl ketene dithioacetal **1a** with ethyl cyanoacetate under all of the above conditions.

Table 1 Screening of reaction conditions [a]



1a **2a** **3a**



4a

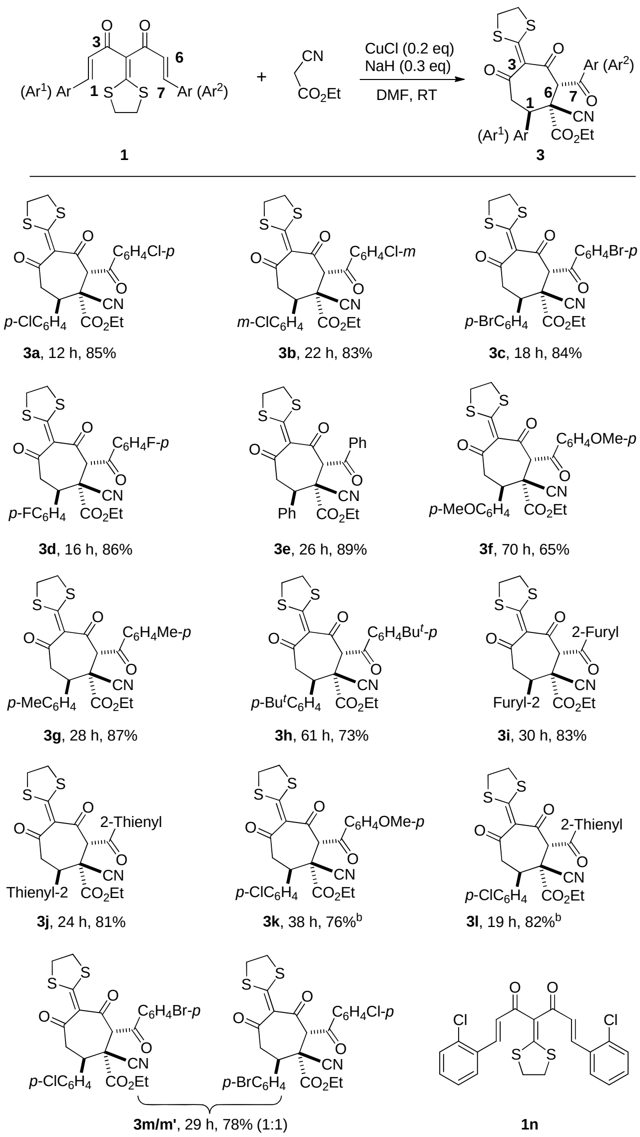
entry	solvent	base [equiv]	catalst	time [h]	yield [%][a]	
					2a	**3a**
1[b]	EtOH	NaOH (1.0)		24		
2[c]	DMF	DBU (0.1)		4	75	
3	DMF	DBU (0.3)	CuCl	20		83
4	DMF	DBU (0.3)	$CuCl_2$	20	10	68
5	DMF	DBU (0.5)	$CuCl_2$	12		85
6	DMF	DBU (0.5)	$CuBr_2$	48	22	75
7	DMSO	DBU (0.3)	CuCl	20	50	42
8[d]	MeCN	DBU (0.3)	CuCl	20		
9[e]	EtOH	DBU (0.3)	CuCl	24		
10	DMF	Et3N (0.3)	CuCl	24	14	50
11	DMF	NaOH (0.3)	CuCl	24	11	70
12	DMF	NaH (0.3)	CuCl	12		85

[a] Isolated yields. [b] The reaction was carried out at 45 °C, **1a** was recovered in 95% yield. [c] **1a** was recovered in 20% yield. [d] **1a** was recovered in 89%. [e] No reaction.

Significantly, the formation of the seven-membered ring compound **3a** indicates that ketene dithioacetal **1a** can also act as the acyclic C_6 synthon, even though it is a classical C_7 1,7-dielectrophile as described in our previous report.[9] Thus, under the optimal reaction conditions (Table 1, entry 12), the scope of dicinnamoyl ketene dithioacetals **1** for the direct construction of **3** was investigated and the results are summarized in Table 2.

It was observed that the reactions of ethyl cyanoacetate with symmetrical dicinnamoyl ketene dithioacetals **1** with electronically varied aryl groups, such as electron-deficient aryl groups (**1a**–**d**), phenyl (**1e**), electron-rich aryl groups (**1f**–**h**),[12] and heteroaryl groups (**1i** and **1j**) at the 1,7-positions (β-positions of the enone moiety) can afford the corresponding seven-membered ring products **3a**–**j** in high to excellent yields. It is important to note that all the above reactions proceed in a highly diastereoselective manner (Table 2). In addition, longer reaction times were required with increasing electron-donating ability of the function groups on the 1,7-aryl rings, indicating, similar to the previous report,[9] that **1** having electron-deficient aryl groups at the 1,7-positions are more reactive than those bearing electron-rich aryl groups in the oxidative [6+1] annulation reaction (Table 2).

Table 2 Synthesis of cycloheptane-1,3-diones **3**[a]

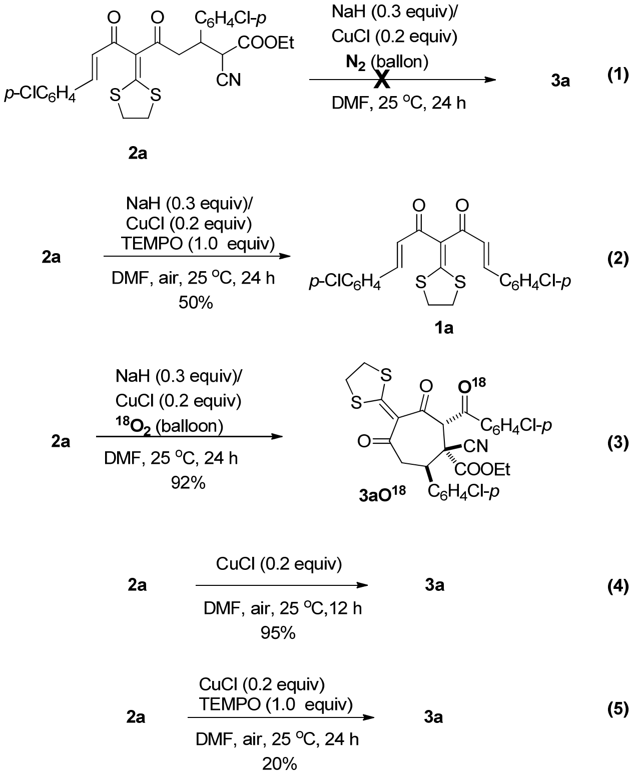


3a, 12 h, 85% **3b**, 22 h, 83% **3c**, 18 h, 84%
3d, 16 h, 86% **3e**, 26 h, 89% **3f**, 70 h, 65%
3g, 28 h, 87% **3h**, 61 h, 73% **3i**, 30 h, 83%
3j, 24 h, 81% **3k**, 38 h, 76%[b] **3l**, 19 h, 82%[b]
3m/m', 29 h, 78% (1:1) **1n**

[a] Isolated yields. [b] Only one diastereomers was obtained.

Furthermore, the desired products **3k**, **3l** and **3m/3m'** were also prepared in high yields under identical conditions using non-symmetrical substrates **1k**–**1m** as the C_6 synthons, respectively (Table 2).[13] However, dicinnamoyl ketene dithioacetal **1n**, bearing a chlorine atom at the *ortho*-position of each phenyl ring, was inert to form either the desired mono-Michael adduct **2o** or seven-membered ring product **3o** under identical reaction conditions as above even for 36 h due to probably the steric hindrance of the 2-chloro-phenyl groups.[9]

All the above results (Table 1 and 2) indicate that the formation of seven-membered ring products **3** requires a tandem approach involving, probably, the Michael/intramolecular anti-Michael addition[14]/aerobic benzylic oxidation sequence or a radical mechanism.[10] Thus, to gain more information on the reaction mechanism, several reactions were carried out using mono-Michael adduct **2a** as a probe, with results as shown in Scheme 2.

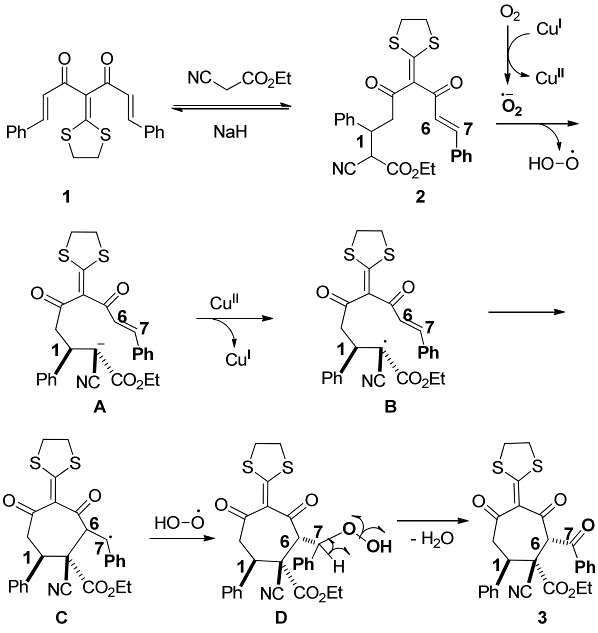


Scheme 2 Mechanism studies.

It was observed that: (1) under a nitrogen atmosphere, no **3a** could be observed by treatment of **2a** under otherwise optimal conditions (as in Table 1, entry 12) for 24 h (Scheme 2, eqn 1), indicating that molecular oxygen plays a crucial role for the intramolecular cyclization of **2a**; (2) in the presence of 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO, 1.0 equiv) as radical scavenger, the reaction of **2a** gave dicinnamoyl ketene dithioacetal **1a** in 50% yield *via* retro-Michael addition along with the recovery of **2a** in 45% yield (Scheme 2, eqn 2), indicating a radical mechanism; and (3) under an $^{18}O_2$ atmosphere, the above reaction led to the formation of **3aO^{18}** in excellent yield (Scheme 2, eqn 3).

It was also observed that: catalyzed by CuCl, the reaction of **2a** afforded **3a** in excellent yield under identical reaction conditions as above but in the absence of NaH (Scheme 2, eqn 4). This result demonstrates that an external base is not needed to promote the transformation from **2a** to **3a** *via* an intramolecular radical cyclization (Scheme 2, eqn 1–3). In addition, it was proved that, in the presence of TEMPO (1.0 equiv), the CuCl-catalyzed reaction of **2a** gave **3a** in 20% yield along with the recovery of **2a** in 61% yield (Scheme 2, eqn 5).

The above results demonstrate that the intramolecular cyclization/benzylic oxidation process of **2a** (instead of an anti-Michael addition)[14] should occur in the presence of both CuCl catalyst and molecular oxygen (Scheme 2, eqn 4) because no the desired seven-membered ring product **3a** can be obtained in the absence of either oxygen molecule (Scheme 2, eqn 1) or CuCl (Table 1, entry 2). Accordingly, it is reasonable to explain the present results as showing in Scheme 3 (with the transformation of **1e** to **3e** as an example), which includes: 1) the activation of molecular oxygen by Cu^{I} to give peroxide radical anion,[10,15] which abstracts the proton of mono-Michael adduct **2** to deliver carbanion intermediate **A** and hydroperoxide radical along with the generation of Cu^{II} species; 2) oxidation of carbanion **A** by Cu^{II} *via* single electron transfer (SET) to form radical intermediate **B** with regeneration of Cu^{I} catalyst; 3) intramolecular radical cyclization[16] of **B** (7-*exo*-trig atthe C6-position)[17] leading to benzyl radical intermediate **C**, which reacts with hydroperoxide radical to furnish intermediate **D**; and 4) finally, product **3** is formed by oxidation of the benzyl C(sp^3)–H bond along with the release of water (Scheme 3). The high diastereoselectivity in the present reaction might result from the deprotonation/protonation process of the CH acidic position of C6.



Scheme 3 Proposed mechanism for formation of **3**.

Therefore, the construction of cycloheptane-1,3-dione derivatives **3** from dicinnamoyl ketene dithioacetals **1**, ethyl cyanoacetate, and molecular oxygen can be defined as a new domino process, involving three chemical transformations: base-promoted Michael addition, intramolecular 7-*exo*-trig radical cyclization and subsequent benzylic C(sp^3)–H bond oxidation catalyzed by CuCl in the presence of molecular oxygen (Scheme 3). The present reaction can tolerate electronically varied aryl groups (Table 2) and thus, hopefully, finds extensive usage in organic synthesis.

In conclusion, we have developed an efficient aerobic oxidative [6+1] annulation strategy for the construction of seven-membered carbocycles from the reaction of ethyl cyanoacetate with the 1,7-dielectrophilic dicinnamoyl ketene dithioacetals as the acyclic C_6 synthons. This reaction features high to excellent yields, extremely mild reaction conditions, excellent diastereoselectivity, perfect atom-economy, readily available starting materials and using molecular oxygen as the oxidant. This oxidative [6+1] annulation strategy opens a new way to explore the construction of medium sized rings from easily available acyclic building blocks, further investigations are in progress.

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