

Silver-Mediated Oxidative C–H/C–H Functionalization: A Strategy To Construct Polysubstituted Furans

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Supporting Information

ABSTRACT: A novel silver-mediated highly selective oxidative C-H/C-H functionalization of 1,3-dicarbonyl compounds with terminal alkynes for the creation of polysubstituted furans and pyrroles in one step has been demonstrated. Promoted by the crucial silver species, perfect selectivity and good to excellent yields could be achieved. This protocol represents an extremely simple and atomeconomic way to construct polysubstituted furans and pyrroles from basic starting materials under mild conditions.

he direct utilization of two different hydrocarbons as ▲ reagents for coupling reactions to form C−C bond (C− H/C-H functionalization) is of great significance and a challenge, and application of these strategies to construct polysubstituted furans is especially attractive. The possibility of direct C-H functionalization, especially the oxidative coupling between two C-H bonds, provides a highly attractive strategy for an ideal chemical synthesis.¹ Although some progress has been made in this emerging field,^{1,2} there still remains a great challenge in achieving a highly efficient and selective cross-coupling utilizing two different hydrocarbons as the reagents. A typical example is related to the oxidative coupling of an acetylene C-H bond and other types of C-H bonds. This is due to the facile homocoupling of terminal alkynes in most cases under the oxidative conditions (Glaser-Hay coupling).³ Recently, some insights for the alkynylation of aryl, alkyl C-H and N-H, P-H bonds have been reported.^{1f,4} One often employs a large excess of reagents (vs terminal alkynes) or conducts the reactions by using a syringe pump to partially address the challenge. Improving the synthetical efficiency is still imperative.

Polysubstituted furans and pyrroles not only represent an important class of five-membered heterocycles prevalent in natural products, pharmaceuticals, and agrochemicals (Scheme 2) but also represent useful intermediates in organic synthesis.⁵ In spite of the myriad methods available for constructing the furan and pyrrole scaffold, $S^{c-e,6}$ the direct, region-defined synthesis of polysubstituted furans and pyrroles from basic chemical materials has always drawn chemists' attention. Herein, we would like to communicate our results regarding a silver-mediated highly selective oxidative C–H/C–H functionalization reaction between 1,3-dicarbonyl compounds and terminal alkynes, which illustrated an efficient example of achieving polysubstituted furans and pyrroles in one step under mild conditions (Scheme 1).

Due to the interest in α -functionalization of carbonyl compounds,⁷ recently we focused on the direct alkynylation

Scheme 1. Silver-Mediated Oxidative C-H/C-H Functionalization Route to Polysubstituted Furans



reaction. Undoubtedly, the best choice in constructing a C_{sp} - C_{sp} ³ bond is the direct C_{sp} -H and C_{sp} ³-H functionalization by using carbonyl compounds and terminal alkynes. Our initial efforts focused on the reaction of phenylacetylene **1a** and ethyl acetoacetate **2a**. Using copper salts as the promoter, most of the reactions afforded the homocoupling 1,4-diphenylbuta-1,3-diyne as the major product. To our delight, simply changing Cu salts to Ag salts in the reaction, a new product with the furan structure was obtained in perfect selectivity and moderate yield (Scheme 1 and Table 1). It is reasonable that, in the presence of silver species, the cycloisomerization process could be facile.⁸ This unanticipated and interesting one-step transformation to the polysubstituted furans encouraged us to further examine the feasibility to the efficient furan synthesis.

The combination of Ag₂CO₃ and KOAc in DMF at 80 °C was found to be the best reaction conditions for this Ag-mediated oxidative C-H/C-H functionalization (Table 1, entries 1 and 16-17). Ag_2O could also provide the furan product, but other Ag(I)salts such as AgOAc and AgI were totally ineffective (Table 1, entries 2-4). The polar solvent such as DMSO also gave the desired products but in low yield, while no reactions occurred in THF and toluene (Table 1, entries 5–7). Cs_2CO_3 and K_2CO_3 turned out to be effective while reducing the yields obviously (Table 1, entries 8 and 9). Meanwhile, diluting the reaction could dramatically improve the yields due to the better stirring of the reaction mixture (Table 1, entry 10 vs 1, and entries 15-17). Notably, the employment of a 1:1 ratio between 1a and 2a could also afford the product with perfect selectivity in moderate yield (Table 1, entry 11). Employing just 2- or 3-fold 2a could enhance the conversion of 1a satisfactorily (Table 1, entries 10 and 12). A lesser amount of Ag₂CO₃ would reduce the reaction yield (Table 1, entry 13), but 3.0 equiv of Ag₂CO₃ did not improve the yield compared with 2.0 equiv of Ag_2CO_3 (Table 1, entries 12 and 14).

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Table 1. Conditions Optimization for Silver-Mediated Oxidative C-H/C-H Functionalization of 1a and 2a^a

	(o o	[Ag], base	, solvent		CO ₂ Et
Ph		OEt	80°C, N	l ₂ , 12 h	Ph	~
1a		2a			3aa	
entry	[Ag]	base	solvent	1a:2a	V (mL)	yield $(\%)^a$
1^b	Ag ₂ CO ₃	KOAc	DMF	1:2	4	70
2	Ag ₂ O	KOAc	DMF	1:2	4	48
3	AgOAc	KOAc	DMF	1:2	4	0
4	AgI	KOAc	DMF	1:2	4	0
5	Ag_2CO_3	KOAc	DMSO	1:2	4	48
6	Ag_2CO_3	KOAc	THF	1:2	4	0
7	Ag_2CO_3	KOAc	toluene	1:2	4	0
8	Ag_2CO_3	Cs ₂ CO ₃	DMF	1:2	4	40
9	Ag_2CO_3	K ₂ CO ₃	DMF	1:2	4	24
10 ^c	Ag_2CO_3	KOAc	DMF	1:2	4	87
11	Ag_2CO_3	KOAc	DMF	1:1	4	50
12	Ag_2CO_3	KOAc	DMF	1:3	4	94
13^d	Ag_2CO_3	KOAc	DMF	1:3	4	69
14^e	Ag_2CO_3	KOAc	DMF	1:3	4	93
15	Ag_2CO_3	KOAc	DMF	1:3	5	94
16	Ag ₂ CO ₃	KOAc	DMF	1:3	6	96 (89)
17	Ag_2CO_3	KOAc	DMF	1:3	8	100 (92)

^{*a*}Yield determined by GC analysis with biphenyl as the internal standard. Isolated yields for entries 16 and 17 in the parentheses. ^{*b*}Reactions were carried out on the scale of 0.5 mmol of 1a in the presence of 2.0 equiv of [Ag] and 2.0 equiv of base in 4 mL of solvent in Schlenk tubes at 80 °C for 12 h (entries 1–9). ^cReactions were carried out on the scale of 0.25 mmol of 1a in the presence of 2.0 equiv of Ag₂CO₃ and 2.0 equiv of KOAc in DMF in Schlenk tubes at 80 °C for 12 h (entries 10–17). ^{*d*}1.5 equiv of Ag₂CO₃. ^{*e*}3.0 equiv of Ag₂CO₃.

The reaction was highly selective. For the oxidative reactions involving a terminal alkyne, one often employed an excess of the other substrate to suppress the homocoupling of the terminal alkyne and achieve high selectivity, or even conducted the reactions by using a syringe pump.^{4e,9} In this oxidative C-H/C-H functionalization, no alkyne homocoupling product was observed (even the ratio of the two substrates was 1:1 and added in one pot).

Varied 1,3-dicarbonyl compounds were suitable reaction partners with phenylacetylene 1a to form the polysubstituted furans (Table 2). Promoted by Ag₂CO₃₁ almost all of the β -keto esters are effective under the standard conditions. As shown in Table 2, methyl, tert-butyl, n-otcyl, benzyl, and cyclohexyl acetoacetates all reacted smoothly affording the desired products in good to excellent yields (Table 2, 3ab-3af). Ethyl isobutyrylacetate was also suitable for this reaction (Table 2, **3ag**). In addition, β -diketones could be readily introduced in the reaction, providing the corresponding furans 3ah, 3ai, and 3aj, but the yields were lower. A 1,3-dicarbonyl compound bearing an amide group was also allowed to react with phenylacetylene 1a and afford the furan product 3ak in 65% yield. Interestingly, the reaction of 4-methyl-3-oxopentanenitrile with 1a resulted in a mixture of the two regioisomeric products 3am in 46% yield (ratio = 5:1). Unfortunately, diethyl malonate and 2-nitro-1-phenylethanone were not suitable for the reaction under the current conditions (Table 2, 3al and 3an).

Varied terminal alkynes were also suitable partners with 1,3dicarbonyl compound **2a** to access the polysubstituted furans (Table 3 and eq 1). The reaction was readily extended to a Table 2. Substrates Scope for the Silver-Mediated Oxidative C-H/C-H Functionalization of 1a and 1, 3-Dicarbonyl Compounds 2^a



"Reactions conditions: 0.25 mmol of 1a and 0.75 mmol of 2 in the presence of 2.0 equiv of Ag_2CO_3 and 2.0 equiv of KOAc in 6 mL of DMF in Schlenk tubes at 80 °C for 12 h. Isolated yields. ^bReaction was carried out on the scale of 0.5 mmol of 1a; isolated combined yield; ratio was determined by GC-MS.

variety of aryl terminal alkynes in high yields. Both electronwithdrawing and -donating substituted groups were well tolerated under the conditions, such as Me, Et, *t*-Bu, OMe, COOEt, CN, and Ac groups (Table 3, **3ba**–**3da**, **3ha**–**3ka**). Aryl alkynes bearing halo substituted groups such as fluoro, chloro, and bromo could also be introduced to give the desired corresponding furans (Table 3, **3ea**–**3ga**). Moreover, alkynes containing thiophene and naphthalene moieties could also be employed to the furan scaffold without any difficulties (Table 3, **3la** and **3ma**).

Although good to excellent yields were achieved by the reaction of aryl terminal alkynes and β -keto esters, unfortunately, most of the alkyl terminal alkynes did not perform well under the current conditions. A selected example was shown in eq 1 in which prop-2-ynyl pivalate **1n** could afford the target furan **3na** albeit in a lower yield.



Table 3. Substrates Scope for the Silver-Mediated Oxidative C-H/C-H Functionalization of Aryl Acetylenes 1 and Ethyl Acetoacetate $2a^{a}$



^{*a*}Reactions conditions: 0.25 mmol of 1 and 0.75 mmol of 2a in the presence of 2.0 equiv of Ag_2CO_3 and 2.0 equiv of KOAc in 6 mL of DMF in Schlenk tubes at 80 °C for 12 h. Isolated yields.

Notably, polysubstituted pyrroles could also be achieved via this oxidative C-H/C-H functionalization (eq 2). The multisubstituted pyrrole is a basic scaffold of numerous biologically active alkaloids and pharmaceutical drugs, such as the hugely successful and valuable molecule Lipitor (Scheme 2).

Scheme 2. Examples of Significant Furan- and Pyrrole-Containing Pharmaceuticals



To our delight, simply changing β -keto esters to enamines could readily provide the desired pyrrole products under similar conditions. A selected example (eq 2) shows that a moderate yield of **3ao** could be obtained by the reaction of (*Z*)-ethyl 3-(phenylamino)but-2-enoate **2o** and **1a** in DMSO.

The silver salts could be recycled.¹⁰ One inevitable problem in this reaction was related to the employment of stoichiometric Ag_2CO_3 . Although Ag_2CO_3 is one of the



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cheapest silver sources, we sought to reduce the cost and waste. Actually, excess Ag_2CO_3 and all silver species after the reaction could be recycled conveniently by filtration and treating with nitric acid and Na_2CO_3 . The regenerated Ag_2CO_3 could still promote this oxidative C-H/C-H functionalization in comparable yield without loss of activity (Scheme 3).

Scheme 3. Recovery Experiment of Ag Salts



To gain some preliminary understanding of the mechanism, we synthesized the silver acetylide¹¹ and investigated its reaction with 2a under the standard conditions. The results were listed in Scheme 4. In the presence of additional Ag₂CO₃,

Scheme 4. Reaction of Silver Phenylacetylide and 2a

Ph	٠	29	KOAc	322
		20	DMF, 80°C, N ₂ , 12 h	Jaa
	Without additional Ag ₂ CO ₃			GC Yield 14%
	With additional Ag ₂ CO ₃ (2.0 equiv)			GC Yield 55%

silver phenylacetylide could react with 2a and afford the furan product in moderate yield. Without the additional silver oxidant, the reaction yield was lower. Meanwhile, some internal alkynes have also been tested in the reaction instead of terminal alkynes. However, only a trace of corresponding products could be observed (see more details in the Supporting Information). These results indicated that silver acetylide might be the intermediate in the reaction, and the additional silver oxidant must be needed to achieve this oxidative coupling. Notably, high-valent transition metal induced oxidative radical cyclizations between 1,3-dicarbonyl compounds and alkenes are already known in literature, and the mechanism was regarded as a radical process.¹² By employing styrene as the substrate instead of 1a to react with 2a under the standard conditions, no corresponding dihydrofuran product was produced. These results showed that the mechanism of this silver-mediated oxidative protocol might not proceed via the previous oxidative radical cyclization.

In summary, we have developed a novel silver-mediated highly selective oxidative C-H/C-H functionalization of 1,3dicarbonyl compounds with terminal alkynes, which provided a direct and efficient entry to the polysubstituted furans and pyrroles in one step. Promoted by the crucial silver species, perfect selectivity and good to excellent yields could be achieved in this reaction. From the synthetic point of view, this protocol represents an extremely simple and atom-economic way to construct polysubstituted furans and pyrroles from basic

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starting materials under mild conditions. Meanwhile, the recovery experiment of silver species could dramatically reduce the cost and waste which would allow for a large range of applications in the organic synthesis. Indeed, we believe that silver can act as a "key promoter" in such oxidative cross-coupling reactions involving acetylene C–H functionalization. Further mechanistic studies related to this oxidative transformation are currently underway in our laboratory.

ASSOCIATED CONTENT

S Supporting Information

Experiment details and spectral data for all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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