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Silver oxide(I) promoted Conia-ene/radical cyclization for a straightforward access to furan derivatives

Bao Yu^b, Selkti Mohamed^a, Janick Ardisson^a, Marie-Isabelle Lannou^{*a}, Geoffroy Sorin^{*a}

A novel access to fused furan cores using silver oxide(I) has been developed. Mechanistic investigations would indicate the involvement of a Conia-ene reaction/radical cyclization for an expedient path to complex furan derivatives. The reaction is broad in scope with interesting atom economy and can also be conducted in a one-pot fashion from readily accessible α - β -unsaturated ketones.

Furan-based frameworks are main heterocyclic compounds, encountered in a broad array of natural products as well as in pharmaceuticals and polymers.¹ In addition, furan derivatives represent valuable intermediates in organic chemistry as they participate, for example, in total synthesis of complex molecules.² To this aim, despite the numerous routes to access furans or substituted furans, the development of new, efficient, and innovative pathways have to be considered.³ Among these several approaches, transition metal promoted synthesis of furan derivatives constitutes a powerful method⁴ and especially using "coinage" metals.^{5, 6} However, in most cases, precursors may suffer from tedious multi-step synthesis and purification. Additionally, some of these transformations require a transitory leaving group for their promotion, rendering them, in an eco-compatibility and carbon footprint point of view, less attractive. In 2012, Lei's group answered this problem through an elegant strategy using silver mediated oxidative C-H/C-H coupling involving alkynes and 1,3-dicarbonyl compounds, allowing the synthesis of furan derivatives with a perfect atom economy.⁷ Two years later, Song and You reported a similar approach using a gold catalyst for the synthesis of 3-alkynyl polysubstituted furans.⁸ In parallel to the C-H activation, another practical way would consist in the elaboration of a method using readily accessible substrates, simple and mild conditions, without requiring a leaving group strategy.

In a precedent work, we highlighted the ability of Ag₂O/DBU combination to induce isomerization of alkynyl silver into allenyl silver.⁹ This species could react with various ketones leading to dihydrofuran-containing frameworks (Figure 1). In the course of our investigations, while applying these conditions to an enolisable ketone, the reaction led to a furan derivative, therefore involving another mechanism. Based on this result, we would like to disclose herein the unique sequence: conia-ene/radical ring closure reaction for a mild, efficient and straightforward access to polysubstituted furans from readily available terminal alkynes.

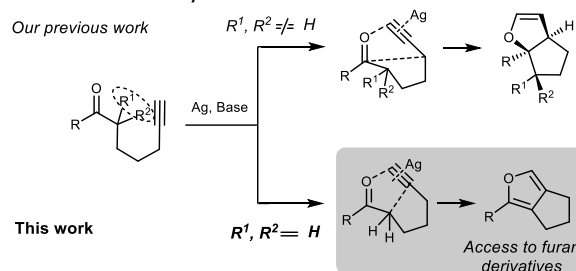


Figure 1: New approach for furan derivatives synthesis

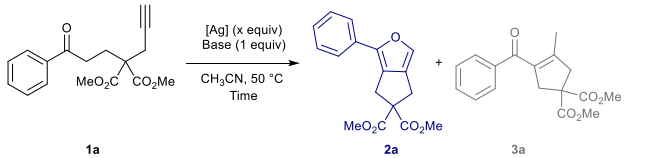
Since its discovery by Conia and Le Perchec,¹⁰ numerous conditions have been developed for Conia-ene reactions. Most of them involve 1,3-dicarbonyl compounds thanks to their enolization ability.¹¹ However, performing such cyclization from "unactivated" ketones turn out to be more difficult since they possess a significantly lower enol/ketone equilibrium than their 1,3-dicarbonyl counterparts.¹² Thenceforth, Conia-ene reaction on this type of substrates require harsher methods such as catalysis by means of transition metal/Frustrated Lewis pair catalysis¹³, transition metal/organocatalysis combination¹⁴ or the concomitant utilization of transition metal/silyl enol surrogate.¹⁵ As a conclusion, efficient Conia-ene type cyclization for the synthesis of furan derivatives from unactivated ketones proves to be highly challenging and has, to the best of our knowledge, never been described so far. Since silver salts can act as a dual catalyst by σ - and π -acid activation,¹⁶ we postulated that the combination of silver salt and base would be able to concomitantly promote deprotonation/isomerization/C-C triple bond activation steps required for furan synthesis derivatives.

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To assess the feasibility of such transformation, we submitted the enolizable ketone **1a** to a range of silver salts in combination with a base in a variety of solvents.

Table 1: Optimisation of the reaction.

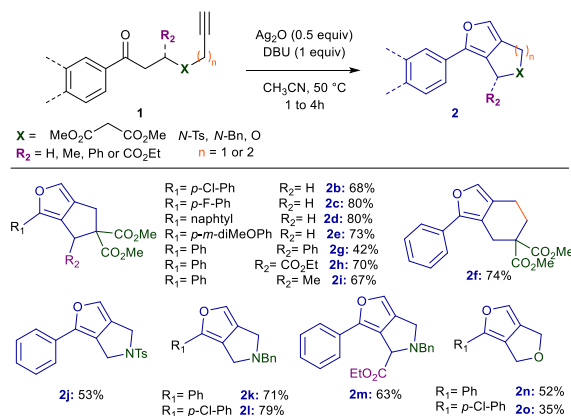


Entry	[Ag]	Base	Solvent	Time ^a	¹ H NMR yield ^b 2a/3a
1	AgNO ₃ 1 eq	DBU	CH ₃ CN	24 h ^c	24% / 4%
2	Ag ₂ CO ₃ 0.5 eq	DBU	CH ₃ CN	2 h	53% / 5%
3	AgOTf 1 eq	DBU	CH ₃ CN	2 h	44% / 4%
4	AgNTf ₂ 1 eq	DBU	CH ₃ CN	2 h	70% / 7%
5	Ag ₂ O 0.5 eq	DBU	CH ₃ CN	2 h	75% / -
6	Ag ₂ O 0.5 eq	K ₂ CO ₃	CH ₃ CN	24 h ^c	40% / 8%
7	Ag ₂ O 0.5 eq	NEt ₃	CH ₃ CN	24 h ^c	66% / 3%
8	Ag ₂ O 0.5 eq	DBU	DMF	2 h	62% / 3%
9	Ag ₂ O 0.5 eq	DBU	THF	3 h	66% / 3%
10	Ag ₂ O 0.5 eq	DBU	MeOH	3 h	20% / 2%
11	Ag ₂ O 0.5 eq	-	CH ₃ CN	24 h ^c	19% / 2%
12	-	DBU	CH ₃ CN	24 h	n.r

^a The reaction was monitored by TLC. ^b ¹H NMR yield was determined from 1,3,5-trimethoxybenzene as internal standard. ^c Not complete after 24h.

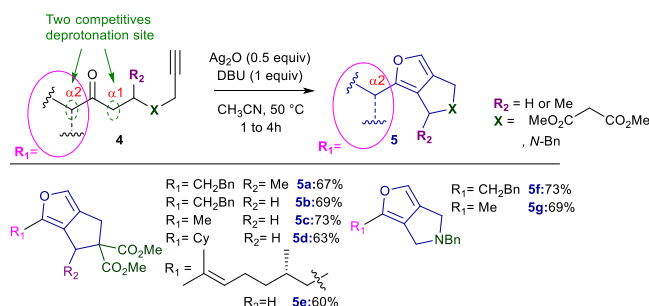
To our delight, using the couple AgNO₃/DBU in CH₃CN at 50°C allowed a low but encouraging conversion of ketone **1a** into the desired furan derivative **2a** after 24h (**entry 1**: 24% by ¹H NMR). Traces of the ketone **3a** (**entry 1**: 4%), probably resulting from a Conia-ene reaction and subsequent isomerization were also detected. Ag₂CO₃ and AgOTf provided **2a** in a similar yield (respectively 53 % and 44 % (**entries 2** and **3**) whereas AgNTf₂ significantly improved the yield in favour of **2a** (70%, **entry 4**). Finally, the best promoter proved to be Ag₂O, affording the expected furan **2a** in 75 % yield without any trace of Conia-ene product (**entry 5**) in only 2h. Using others organic or inorganic bases like K₂CO₃ or NEt₃ turned out to be less effective since 24 hours were necessary to obtain satisfying conversions (**entry 6** and **7**). A short screening of solvents highlighted the propensity of DMF (**entry 8**) and THF (**entry 9**) to cleanly promote the reaction with similar yields in contrast to protic solvent such as MeOH (**entry 10**). Finally, CH₃CN revealed to be the most suitable solvent for this transformation (**entry 5**). Noteworthy, without base, only 19% conversion was obtained after 24 h (**entry 11**), whereas without silver salt, no reaction occurred even after a prolonged time (**entry 12**). These last two experiments underlined the crucial need to combine Ag₂O/DBU for a clean, fast and complete conversion of ketone **1a** into the furan **2a**. At this stage, we were unfortunately unable to run these reactions in a catalytic fashion.¹⁷

With the optimised conditions in hands, we first screened the reactivity of different aromatic ketones (Scheme 1).



Scheme 1 Furan access from aromatic ketones.

Substituted or polysubstituted aromatic ketones afforded the corresponding furans (**2b**, **2c**, **2d** and **2e**) with roughly similar yields (68 to 80%). A longer spacer (4 C length) between the ketone and the alkyne moiety was also well tolerated (compound **2f**). A slight decrease in yield was observed when the ketone was substituted in the β position (**2g**, **2h** and **2i**) especially for compound **2g**-comporting a phenyl ring. This drop in yield may be attributed to a retro-Michael addition due to a steric clash between the two aromatic parts, which seems to be very close in the final structure. Introducing a nitrogen atom instead of dimethyl ester on the chain turned out to be effective leading to fused polyheteroaromatic structures in with very good yields. Noteworthy, the reaction was more efficient when carried out on substrates bearing a *N*-benzyl protected nitrogen (compounds **2k**, **2l** and **2m**) instead of its *N*-tosyl counterpart (compound **2j**). In this latter case, the higher acidity of the proton in α position to the nitrogen may allow partial deprotonation by DBU, allowing side reactions to occur.¹⁸ This reaction has also been successfully extended to oxygenated propargyl derivatives affording dehydrofurofuran cores **2n** and **2o** with moderate yields (respectively 52 and 35%). After this survey, we decided to turn our attention to more challenging ketones having less acidic protons in α-position¹⁹ and exhibiting two enolizable positions (α¹ and α²) (Scheme 2).

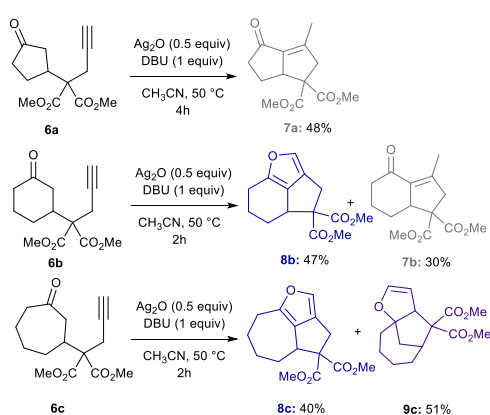


Scheme 2 Furan access from aliphatic ketones.

Using the same conditions as above, we were pleased to obtain similar yields on aliphatic ketones. Thus, ketones **4a** and **4b** afforded the corresponding furans **5a** and **5b** in comparable yields (respectively 67% and 69%). Reaction conducted on less sterically

hindered **4c** or more congested ketones **4d** and **4e** delivered adducts **5c**, **5d** and **5e** respectively in satisfying yields (73%, 63% and 60%) without significant difference. In the same way, *N*-Bn compounds **4f** and **4g** provided furans derivatives **5f** and **5g** in good yields. Moreover, X-ray structure of compound **5g** was performed, confirming the structure and the flat shape adopted by these compounds.²⁰ All these results highlighted that sterically hindered ketones and/or enolizable on both sides (α^1 and α^2) are not deleterious to the reaction. Attack of the α^1 -enolate onto the alkyne is obviously favoured since it leads to the five-membered ring adduct whereas attack of α^2 -enolate would provide the corresponding seven-membered ring compound.²¹

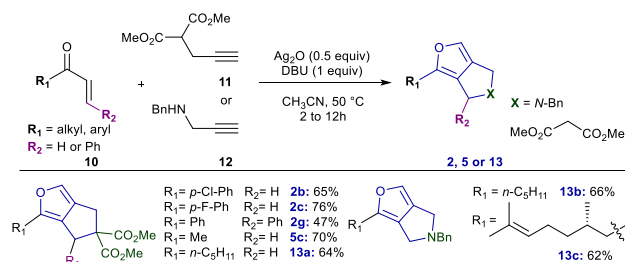
We next decided to submit cyclic ketones to $\text{Ag}_2\text{O}/\text{DBU}$ combination in order to get access to fused tricyclic complex furan derivatives (Scheme 3).



Scheme 3 Furan access from cyclic ketones.

As expected, due to ring strain, ketone **6a** did not provide the furan derivative and only the α,β -unsaturated ketone **7a**, probably resulting from a sequence Conia-ene/isomerization reaction, was isolated (48% yield). This Conia-ene adduct (**7b**) was also observed (30%) when the reaction involved ketone **6b** but we were pleased to obtain the highly strained tricyclic furan **8b** as the major product (47%). Hence, to date, this type of furan core was only accessible by using Rh/carbene chemistry²² or photocycloaddition.²³ Finally, the seven-membered ring analog **8c** was also obtained in a similar range of yield (40%) from ketone **6c**. Nevertheless, in this latter case, the major compound was the tricyclic dihydrofuran **9c** (51%). Presence of this adduct would suggest the formation and the competitive reaction of a silver allenyl intermediate onto the ketone as observed in our previous methodology.⁹

In order to render this transformation more step economic, we focused on a one-pot procedure since DBU has formerly been identified by Kim and co-workers as an efficient base for the promotion of Michael addition reactions.²⁴ Hence, the base could initially allow the 1,4-addition onto the α,β -unsaturated ketone prior to the cyclization process. To this aim, we applied our optimized conditions to various readily available Michael acceptors in the presence of either propargyl malonate **11** or propargyl amine derivative **12** (Scheme 4).



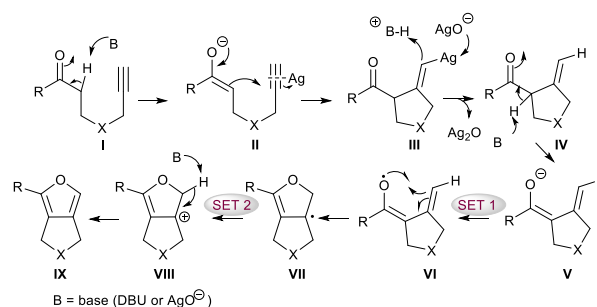
Scheme 4 One-pot process.

To our delight, our cyclization conditions were found suitable for a one-pot process and similar yields were obtained for **2b**, **2c**, **2g** and **5c** to those reported in scheme 1 and 2. Additionally, three others new furans (**13a**, **13b** and **13c**) were provided with a satisfying yield (respectively 64 %, 66 % and 62 %) using this direct route from commercial or easily available substrates.

Astonishingly, cyclization trials conducted on structurally close substituted alkynes as well as reactions performed in intermolecular fashion between ketone and terminal alkyne led to messy crude mixtures, where the presence of the expected compounds was not detected whatever the conditions.²⁵

In order to explain the formation of these furan derivatives, we postulated the mechanism depicted in Scheme 5.

Scheme 5.



Scheme 5 Postulated mechanism.

First of all, deprotonation of the ketone **I** and concomitant activation of the alkyne moiety by silver derivative would promote the first ring closure by means of a Conia-ene reaction (**II**). Vinyl silver intermediate **III** would then be reprotonated with concomitant silver oxide(I) regeneration, leading to homoallylic ketone **IV**. A second deprotonation step would generate the enolate **V** which could undergo a first SET by oxidation with Ag_2O (**VI**). A 5-endo-trig radical cyclization²⁶ would furnish the stabilized allylic radical **VII** followed by a second SET leading to the stabilized cation **VIII**. Finally, a deprotonation step would allow the access to the furan moiety **IX**. To gain insight into the mechanism, control experiment was conducted. Performing the reaction in the presence of TEMPO as radical trapping agent afforded similar yields but dramatically slowed down the reaction rate (12h instead of 2h without TEMPO). Noteworthy, previous studies using TEMPO showed that, if radical process occurs intramolecularly or if the radical reaction rate is fast, the radical scavenger may encounter difficulties in trapping it, which could explain our result.²⁷ In addition, during the reaction, we observed a black precipitate which was characteristic of silver

nanoparticles, known to promote SET from alkoxides.²⁸ Indeed, silver oxide(I) promoted ring closure through similar SET process was already described.²⁹ Therefore, radical mechanism cannot be ruled out.

Conclusions

In conclusion, we developed an innovative, efficient and straightforward method for the synthesis of complex and original furans derivatives. The procedure described herein is very easy to set-up, shows a very good functional tolerance and affords the expected products in high yields from readily accessible substrates ϵ - or ζ -ketoalkynes, by proceeding with interesting atom economy. Hence, application to natural products or pharmaceuticals synthesis could be envisioned.³⁰ In parallel, this transformation can also be realized in a one-pot fashion with similar efficiency, thus reinforcing the step-economy, this time from commercial or even more easily accessible Michael acceptors and appropriate propargyl derivatives. On a mechanistic point of view, this new transformation would involve a Conia-ene reaction from unactivated ketone as well as a radical cyclization by two successive SET both catalysed by silver oxide(I). However, silver nanoparticles formed during the reaction could also catalyze the radical reaction. These two reactions are very scarcely described in the literature and have never been used for the synthesis of furan derivatives to date. Extension to intermolecular and substituted alkynes are currently under investigation in our laboratory.

Conflicts of interest

Authors declare no conflicts of interest.

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