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A novel cyclization/oxidation strategy for a two-step synthesis of (Z)-aurone

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ABSTRACT

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Keywords: (Z)-aurone Silver (I) nitrate Fétizon oxidation Regio-selectivity Oxygen heterocycles Cascade reaction An efficient and facile two-step strategy for the synthesis of (Z)-aurone from arylacetylenes and salicyladehydes, *via* silver(I) nitrate mediated cyclization/ oxidation in the presence of potassium carbonate has been developed. The key feature of our method was delicate cascade reaction, to provide the corresponding (Z)-aurone in high yield and good regio- and stereo selectivity.

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A number of naturally occurring aurone which possess various hydroxylation patterns, such as sulfuretin (3), aureusidin (4),

maritimetin (5), and bracteatin (6), have numerous biological

activities.⁴ Therefore, formidable efforts have been made on

Previous Method

CSNs^{7c} or Cy₃PAgC^{7d}

or AgCl⁹

This Method

However, some of these approaches suffered from various

limitations such as side reaction,^{5a} low yield,⁶ and long reaction

time.⁷ Although few studies have reported the synthesis of aurones from the precursor 7, they typically used toxic MnO₂

as an oxidant at a later stage as illustrated in Scheme 1.

Moreover, the above methods also required complex silver

Scheme 1. One-pot strategy for synthesis of (Z)-aurone

one-pot

the synthesis of (Z)-aurone and its derivatives.^{5,6,7}

AgNO₃, K₂CO₃ Toluene, reflux

OH

OН.

Introduction

Flavonoids and their derivatives have drawn much attention because many compounds with this skeleton display pronounced biological and pharmaceutical activities.¹ (*Z*)-aurone (1) [(*Z*)-2-benzylidenebenzofuran-3(2H)-one] is a well-known natural product belonging to the sub class of flavonoid family (Figure 1), that contributes to the pigmentation of flowers and fruits.² Aurones have a broad range of bioactivities including antifungal, antioxidation, tyrosinase inhibition, iodothyronine deiodinas inhibition, antitumor and anti-cancer, etc.³



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catalysts and expensive gold catalyst in the cyclization step.^{5c-e, 7} Consequently, it is necessary to find the way to use a simple silver catalyst for the synthesis of aurones without adding any external oxidizing agents.

Over the past decades considerable progress have been made in the development of transition metal catalyzed domino reactions, which are an ideal approach in organic synthesis.⁸ In such reactions, at least two consequent steps occur in one synthetic operation and need not isolate intermediates. Furthermore, these methods hold advantages such as low cost and time saving. Thus, finding a suitable catalyst which can also act as oxidant is highly desirable.

In this manuscript, we describe a simple and an efficient way to synthesize of (Z)-aurone derivatives from easily available starting materials *via* Ag(I) mediated *5-exo-dig* cyclization and subsequent oxidation. This method is advantageous in high yield and good stereoselectivity.

2. Results and discussions

To explore a suitable reaction conditions to probe the feasibility of cyclization/oxidation reaction, 2-(1-hydroxy-3phenylprop-2-ynyl)phenol (7) was selected as a representative substrate; and the results are summarized in Table 1. Our initial effort using AgNO₃ in methanol at room temperature resulted in the formation of a new product. However, it was unsatisfactory because the benzyl propargylic hydroxyl group was converted to a methoxy group to afford compound 10 (Table 1, entry 1). We realized that a base can influence the stability of benzyl propargylic alcohol. Therefore, we successfully utilized 2.2 equiv of potassium carbonate (K2CO3) and 2.2 equiv of AgNO₃ to afford the desired product 9 in 15% yield (Table 1, entry 2). The silver catalyst plays a dual role in this cascade reaction; it activates alkyne during 5-exo-dig addition (cyclization) and subsequently oxidizes the benzylic alcohol to ketone in the presence of K₂CO₃. Encouraged by the results above, we attempted to find appropriate conditions, in the previous study water triggered the synthesis of aurone derivatives,^{5c,e} we have added 1 drop of water, but it could not accelerate the reaction; the yield was only 13% (Table 1, entry 3). The use of 5.0 equiv of AgNO₃ afforded expected product in only 17 %, and rest of the starting material was converted to side products (Table 1, entry 4). Reducing the catalyst loading to 20 mol % it quantitatively afforded the compound **8** with a trace amount of 9 (Table 1, entry 5). The above results suggested that changing methanol to other solvent would be a good option for reducing the generation of side products. Using other polar solvents like DMF, THF, and CH₃CN was not beneficial in the cascade reaction (Table 1, entry 6). Inspired by Fétizon oxidation¹⁰ we realized the importance of using non-polar solvent and avoiding the influence of water. Because cyclization was required, we chose the commonly used solvent toluene (Table 1, entries 7-9).

We found that the use of 2.2 equiv. of $AgNO_3$ and 2.2 equiv of K_2CO_3 in toluene at 120 °C under nitrogen atmosphere afforded the formation of **9** in a higher yield (Table 1, entry 8). We were interested in finding the reaction pathway; the entire pathway is depicted in Scheme 2, which shows that (*Z*)-aurone can be synthesized from 2-(1-hydroxy-3phenylprop-2-ynyl)phenol (7) and the key step is a one-pot cyclization/oxidation reaction. We assumed two possible alternate pathways: oxidation followed by cyclization and, cyclization followed by oxidation. We monitored the reaction by TLC and NMR (supplementary information), which found that the second pathway was dominant; this was also demonstrated by use of 1.0 equivalent of $AgNO_3$ (Table 1, entry 9), which resulted in the appearance of silver mirror.



	он он 7	AgNO ₃ (X ec K_2 CO ₃ (2.2 c conditions	a) eq) s	9	OMe OH 10
Entry	AgNO ₃ (equiv.)	Solvent	Temp (°C)	Time (h)	Yield ^b (%)
1 ^c	2.2	MeOH	rt	3	SR ^d
2	2.2	MeOH	rt	2	15
3	2.2	MeOH/H ₂ O	rt	30 min	13
4	5.0	MeOH	rt	20 min	17
5	0.2	MeOH	rt	2	Trace ^e
6	2.2	Solvents ^f	rt	2	SR/NR ^g
7	2.2	Toluene	rt	24	trace
8	2.2	Toluene	120	2	94
9	1.0	Toluene	120	2	37
10^{h}	2.2	Toluene	120	2	90
11 ⁱ	2.2	Toluene	120	2	92
12 ^c	2.2	Toluene	120	24	trace
13°	0.0	Toluene	140	24	

^a conditions: Unless otherwise stated, all the reactions were conducted in 1.0 equiv. of starting material, 2.2 equiv. of AgNO₃, 2.2 equiv. of K₂CO₃ under nitrogen atmosphere. ^b isolated yield of **9**, ^c absence of base, ^d side reaction, mainly **10**. ^e monitored by TLC. ^f DMF, THF, or CH₃CN was used as a solvent. ^g side reaction or no reaction. ^h 10 mol% TBAI was used as an additive. ⁱ10 mol% Celite was used as an additive.

This experiment indicates initial cyclization with the formation of **8**, followed by oxidation; in the case of oxidation followed by cyclization, we would not obtain final product **9** because the reaction would stop at the oxidation step, resulting in **11**.

Additives did not increase the reaction yield; for instance, the yield was somewhat lowered when we used TBAI¹¹ or celite¹² (Table 1, entries 10, 11). The Fétizon oxidant (Ag_2CO_3) was found to be not suitable for this transformation, as the product was obtained only in trace amount. No desired product was obtained with other catalysts examined such as Cu₂SO₄. FeSO₄ (entries not shown). This reaction also depended on the choice of base. The replacement of K₂CO₃ with NaHCO₃ proved to be inefficient and only trace amount of product was obtained. In the case Et₃N and DIPEA no product formation was observed even the reaction was carried out for a longer time 24 h (entries not shown). From the experiment shown in entry 12, K₂CO₃ is a mandatory base in this reaction, as in its absence only trace amount of product was detected. Omitting both the catalyst and base resulted in no product formation; and the starting material remains intact even at a prolonged reaction time and elevated temperature (Table 1, entry 13). As a result of these finding, we considered the optimal reaction conditions are as follows: 7 (1.0 mmol, 1.0 equiv) with AgNO₃ (2.2 equiv.), K₂CO₃ (2.2 equiv.) in toluene (2.0 mL) under nitrogen atmosphere at reflux temperature for 2 h.

Having established most promising conditions in our hand, we next evaluated substrates with different substitution patterns. We synthesized a variety of substituted aurone



Scheme 2. Synthetic pathway of our strategy

Table 2. Substrate scope^a



^a Conditions: All the reactions were conducted with 1.0 equiv of starting material, 2.2 equiv of AgNO₃, and 2.2 equiv of K_2CO_3 , in toluene (2.0 mL) at 120 °C for 2 h. Yields refers to the isolated yield.

aurone derivatives.¹⁴ As summarized in Table 2; all the reactions were completed within 2 h, and different substituents could be employed in this reaction to afford the desired products in moderate to good yields; either electron-donating

precursors **12a-22a**¹³ to establish the scope of the cascade system and its applicability for synthesizing a wide range of

or electron-withdrawing substituent groups on the phenylacetylene or salicyladehydes were well tolerated. A variety of halogen containing substrates (Cl, Br) were compatible under the standard conditions, providing the expected products in good yields. It is noteworthy that the alkyl-substituted substrates also provide the corresponding products in good vields. For instance, bulky *t*-butyl group on the salicylaldehyde ring could afford the desired product in high yields. It was pleased to find that the substrates bearing strong electron-withdrawing groups such as NO₂ group were also suitable for the reaction, although the yield of the product was lower (31%). An electron-donating group on arylacetylene disfavored the reaction: with MeO- as the substitute, only about 70% of yields of the desired products were observed. While MeO- group on salicylaldehyde ring complete conversion occurred, but the product was decomposed even when it stored at low temperature (-20 °C). Configuration of the aurones was established with the help of NMR spectral data by comparison with the data reported in the literature. All though we did not try all possible substitutions in all positions, it is reasonable to predict on the basis of the previous reported^{5c,d,e,7} and our limited data that most compounds would be synthesized.

Conclusion

We have developed a novel method for the synthesis of (Z)-aurones *via* silver mediated cascade reaction from readily available 2-(1-hydroxy-3-phenylprop-2-ynyl)phenols. It is an example of how to utilize a cascade reaction to solve problems wisely. A series of diversely substituted aurones were synthesized in good yields and shorter reaction time rendering this methodology highly valuable.

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- 13. To a solution of arylacetylene (1.6 mmol) in THF (4.0 mL) was dropwise added *n*-BuLi (1.5 mmol, 2.5 M in *n*-hexane) at -40 °C. After 0.5 h stirring, a solution of corresponding salicylaldehyde (1.0 mmol in 4.0 mL anhydrous THF) was dropwise added at -40°C The reaction mixture was stirred at -40 °C for 2 h and then heated up to 0 °C for 5 min followed by quenched with water. The organic solvent was removed by rotary evaporator and the rest was extracted with EtOAc twice. The collected EtOAc layer was washed with brine, dried over Na₂SO₄, filtered, and evaporated. The crude product was purified by flash column chromatography.
- 14. To the precursors (12a-22a, 0.5 mmol) in anhydrous toluene was added K₂CO₃ (2.2 equiv., 1.1 mmol) at room temperature and then heated to 50 °C. The reaction mixture was stirred for 10 min and AgNO₃ (2.2 equiv., 1.1 mmol) was added, which was rapidly heated till reflux. The reaction was stopped within 2 h, and silver mirror was observed. After cooling down, the solid was removed by filtration with celite, and remove solvent by rotary evaporator. The crude product was purified by flash column chromatography.
- 15. The limitation of our strategy is that the product yield would decrease, when the 6 or 4' position was substituted.

Highlights

- Two-step synthesis of (Z)-Aurones through cyclization/oxidation cascade reaction
- A novel AgNO₃-promoted synthesis of diversely substituted aurones was developed.
- Accembra • (Z)-Aurones were obtained in good yields with excellent regio- and diastereoselectivity.