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One-pot approach to access 2*H*-pyran-2-ones bearing an amino group *via* the Pd-catalyzed Sonogashira coupling of (*Z*)-3-iodovinyl esters followed by intramolecular iodocyclization

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ABSTRACT

A one-pot sequence of Sonogashira coupling and iodocyclization afforded novel amino-containing trisubstituted 2*H*-pyran-2-ones in good yields. This transformation proceeds *via* 1) synthesis of an enoic ester intermediate by a Sonogashira coupling reaction with an *N*-substituted (*Z*)-3-iodovinyl ester; 2) intramolecular iodocyclization of the latter intermediate under mildly basic conditions. The flexibility of this strategy enables the efficient syntheses of a variety of substituted 2*H*-pyran-2-ones.

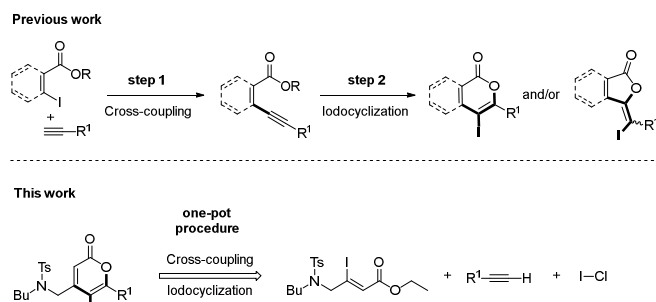
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Introduction

The alkyne bond plays an important role in various organic syntheses and is widely used to prepare diverse heterocyclic derivatives.¹ Among these methods, the iodocyclization reaction between acetylenic and nucleophilic groups has been described for the formation of many important functionalized cyclic compounds.² This methodology occupies a special position in organic synthesis because of its simple manipulation under mild reaction conditions,³ which could be applied to prepare various complex bioactive molecules.

In addition, the synthesis of six-membered oxygen containing heterocycles, such as pyranones, has received considerable attention.^{4, 5} These heterocycles constitute important classes of biologically active structures that present a range of biological and pharmacological uses as, for example, antifungal,⁶ antimicrobial,^{4c, 7} or phytotoxic agents.⁸ Various pyranones have been prepared *via* an intramolecular iodocyclization reaction between ester derivatives and alkyne groups.⁹ In all cases described in the literature, the synthesis of these pyranones starting from alkynes and (*Z*)-3-iodovinyl ester derivatives using palladium catalysts has been reported in two separate steps: (i) coupling of (*Z*)-3-iodovinyl ester derivatives with terminal alkynes, typically *via* a Sonogashira-type reaction, and (ii) enyne iodocyclization (Scheme 1).⁹ Based on the known literature, a synthetic route *via* a one-pot reaction starting from (*Z*)-3-iodovinyl ester derivatives is not known. Therefore, the introduction of an amino group into the structure of the latter is considered an interesting challenge.¹⁰

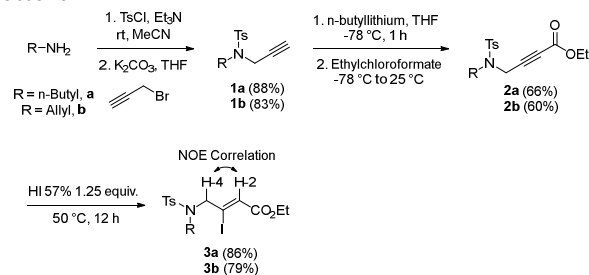


Scheme 1. Synthesis of 2*H*-pyran-2-ones *via* one-pot Sonogashira coupling and iodocyclization.

Considering the importance of one-pot processes as well as related multicomponent reactions in providing efficient organic synthesis, and in continuation of our work to develop one-pot reactions and their application for the preparation of new heterocyclic structures,¹¹ we report herein a regioselective one-pot reaction starting from *N*-substituted (*Z*)-3-iodovinyl esters *via* a Sonogashira coupling/iodocyclization reaction.

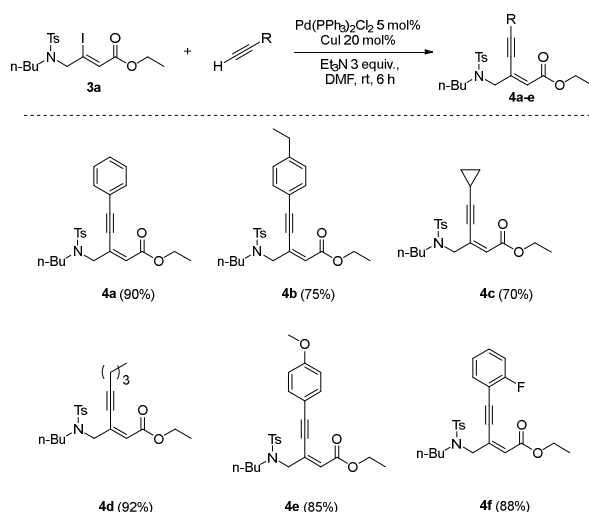
Results and Discussion

The starting esters **3a-b** were prepared in three steps using literature methods according to the sequence illustrated in Scheme 2.¹²⁻¹⁵ The first step of our sequence was the *N*-tosylation reaction of primary amines **a-b** according to the literature.¹² These amines were transformed into **1a-b** with propargyl bromide in the presence of K_2CO_3 as base in THF for 12 hours.¹³ The resulting amines **1a-b** were reacted with commercially available *n*-BuLi 1.6M in hexane at $-78^\circ C$. Addition of the anions to ethyl chloroformate proceeded readily at the same temperature to provide alkynyl carboxylates **2a-b**.¹⁴ Finally, the resulting esters **2a-b** were reacted with hydroiodic acid as reported in the literature to obtain the corresponding (*Z*)-3-iodovinyl esters **3a-b** bearing an amino group in good yields.¹⁵ Stereochemical assignment of the double bond was carried out by NOESY experiments. Diagnostic NOE correlations were observed for H-2 with H-4 in **3a**, which indicated that the double bond is of *Z* configuration (see ESI).



Scheme 2. Synthesis of *N*-substituted (*Z*)-3-iodovinyl ester **3a,b**.

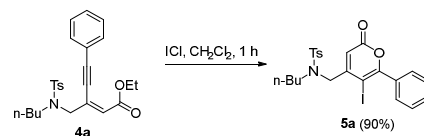
Esters **3a-b** were subsequently used as starting materials for several Pd-catalyzed cross-coupling methodologies using the remaining halogen, to evaluate the effect of the substituted amino group. The use of Suzuki, Heck and Stille coupling procedures led to recovery of the starting material. The most suitable methodology for the derivatization of compound **3a** was the Sonogashira coupling reaction. A copper-co-catalyzed coupling reaction was utilized with $PdCl_2(PPh_3)_2$ (5 mol%) as catalyst and CuI (20 mol%) as co-catalyst in the presence of Et_3N as base in DMF at room temperature. With this protocol, various *N*-substituted enynes **4a-f** were obtained in good yields of 70-92% (Scheme 3).



Scheme 3. Synthesis of *N*-substituted enynes **4a-f**.

The effect of other *N*-substituents on the ester was also investigated. The transformation of ester **3b** carrying an *N*-allyl group into the desired enyne did not proceed under these conditions.

Given the presence of acetylenic group and nucleophilic character of ester, this latter ester **4a** was proven to be a good candidate in the electrophilic cyclization process for the construction of diversely functionalized lactones. Taking advantage of this reactivity, our next step was to transform the obtained β -ethynyl- α,β -unsaturated ester **4a** into the desired lactone after treatment with iodine monochloride in dichloromethane at room temperature (Scheme 4). Under these conditions, the iodocyclization took place quickly leading to the corresponding pyranone **5a** in 90% yield after aqueous work up and subsequent purification by recrystallization.

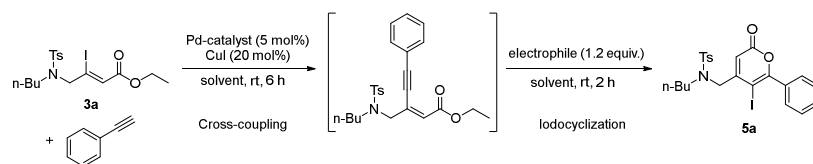


Scheme 4. Iodolactonization of **4a**.

It should be noted that β -ethynyl- α,β -unsaturated esters **4a-e** are unstable. Therefore, esters **4a-e** must be immediately used because they degrade quickly within a few hours even when stored in a refrigerator. On the basis of these observations, we decided to test the construction of these pyranones bearing an amino group by using a one-pot, two-step sequence through a strategy of merging the C-C coupling of *N*-substituted-(*Z*)-3-iodovinyl ester followed by *in situ* iodolactonization. To achieve this goal, we examined the addition of different I⁺ electrophiles such as iodine monochloride (ICl), *N*-iodosuccinimide (NIS), and iodine (I₂) to the triple bond in ester **4a**. We found that the solvent plays a major role on the Sonogashira cross-coupling/iodolactonization sequence. First, when using dichloromethane as the solvent and ICl as an iodinating reagent, a complex mixture was obtained (Table 1, entry 1). We further tested I₂ and NIS in ethanol as electrophiles instead of ICl without changing the other factors (Table 1, entries 2 and 3), but in this case only a complex mixture was obtained. Upon switching to DMF as the solvent, this one-pot procedure

afforded *endo* cyclization product **5a** in 44% yield (Table 1, entry 4). To find the best conditions for this one-pot sequence, the optimization studies were extended by performing this transformation in other solvents. We found that protic solvents such as MeOH, EtOH and *i*-PrOH (Table 1, entries 6–8) showed the best results (60–85%), while the use of aprotic solvents, such as DMF or MeCN (Table 1, entries 4 and 5) resulted in low yields of the desired pyranone **5a** (30–44%).¹⁶ Further tests were carried out with other Pd catalysts such as Pd(PPh₃)₄ and Pd(OAc)₂. The latter was found to be suitable for this one-pot sequence; while the best Pd catalyst was Pd(PPh₃)₂Cl₂ (Table 1, entry 6), Pd(PPh₃)₄ failed to promote this transformation (Table 1, entry 10).

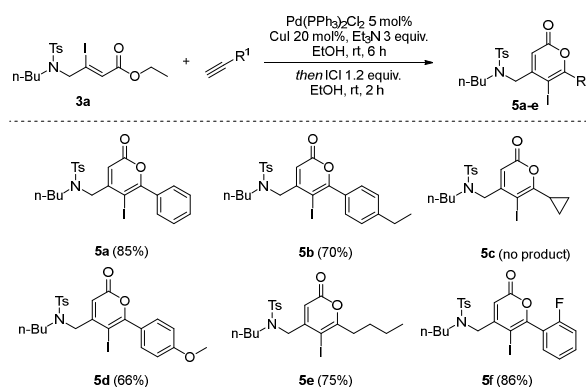
Table 1. Optimization of the one-pot procedure for synthesis of 2*H*-pyran-2-one **5a**.^a



Entry	Catalyst	Solvent	Electrophile	Yield 5a (%) ^b
1	Pd(PPh ₃) ₂ Cl ₂	CH ₂ Cl ₂	ICl	c
2	Pd(PPh ₃) ₂ Cl ₂	EtOH	I ₂	c
3	Pd(PPh ₃) ₂ Cl ₂	EtOH	NIS	c
4	Pd(PPh ₃) ₂ Cl ₂	DMF	ICl	44
5	Pd(PPh ₃) ₂ Cl ₂	MeCN	ICl	30
6	Pd(PPh ₃) ₂ Cl ₂	EtOH	ICl	85
7	Pd(PPh ₃) ₂ Cl ₂	MeOH	ICl	64
8	Pd(PPh ₃) ₂ Cl ₂	<i>i</i> -PrOH	ICl	60
9	Pd(OAc) ₂ + PPh ₃ (20 mol%)	EtOH	ICl	50
10	Pd(PPh ₃) ₄	EtOH	ICl	d

^a Reagents and conditions: phenylacetylene (1.4 mmol), ester **3a** (0.7 mmol), triethylamine (2.1 mmol), catalyst (0.035 mmol), CuI (0.1428 mmol), electrophile (0.84 mmol), rt, solvent (20 mL). ^b Isolated yield. ^c Complex mixture. ^d Starting material.

A range of trisubstituted pyranones **5a-f** were prepared in moderate to excellent yields using the one-pot reaction of *N*-substituted (*Z*)-3-iodovinyl ester **3a** and various aryl and aliphatic terminal alkynes (Scheme 5). Similarly, the use of hex-1-yne gave the desired pyranone **5e** in 75% yield. However, the use of a cyclic alkyne did not give the desired pyranone. All new products were identified using their NMR and HRMS data. It should be noted that the desired products were obtained in a highly regio-controlled manner providing only the 6-*endo*-dig cyclization products as the sole regioisomer. This was supported by the structure of **5a** being unambiguously confirmed by X-ray analysis (Fig. 1, for details see ESI).¹⁷



Scheme 5. Synthesis of trisubstituted 2*H*-pyran-2-ones **5a-f**. Reagents and conditions: **3a** (0.7 mmol), Et₃N (2.1 mmol), CuI (0.14 mmol), PdCl₂(PPh₃)₂ (0.035 mmol), alkyne (1.4 mmol), EtOH (20 mL), rt, 6 h, then ICl (0.84 mmol) in EtOH (2 mL), rt, 2 h.

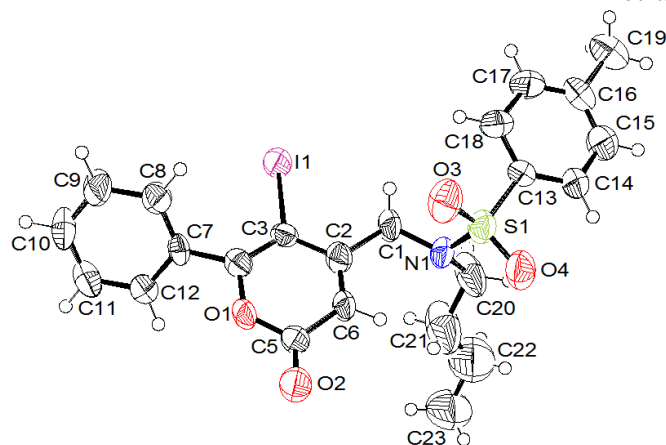


Figure 1. ORTEP representation of **5a** [CCDC1942651] (Thermal ellipsoids are drawn at the 50% probability level).

To explain the regioselectivity, we focused our attention on the charge distribution in the carbon carbon triple bonds in intermediate **4a**, which appear to be critical in determining the resulting cyclization. This was achieved using ab-initio and density functional theory (DFT) calculations using the Turbomole 7.0 programme package (for details see ESI). Two intermediates were selected to emphasize *i*) the charge on each carbon and, *ii*) the impact of the aminomethyl group on the charge distribution. As shown in Figure 2, the natural population analysis of carbons in the alkyne group clearly demonstrates that the presence of the aminomethyl group is a predominant cyclization factor. In the presence of the aminomethyl group, the local charge on the carbon atom leading the 6-ring reaction (denoted β in Fig. 2, charge = + 0.038) is more positive than the other (denoted α in Fig. 2, charge = + 0.013), demonstrating that, according to DFT calculations, the cyclization is expected to occur on the β carbon. On the contrary, in the absence of the aminomethyl group (e.g. substituted by an ethyl group) the local charge on the β carbon atom (charge = + 0.033) is slightly less positive than the α carbon atom (charge = + 0.037), which potentially would allow cyclization on both carbons.

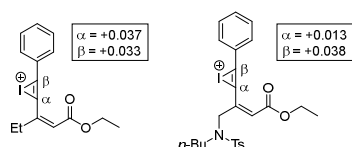
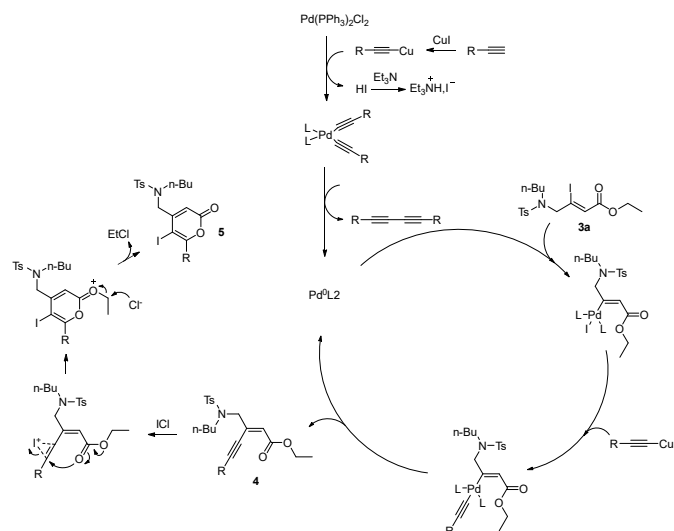


Figure 2. Natural population analysis as a function of the nature of the alkyne substituent.

Based on previous work and our experimental results,⁹ a mechanism for the transformation of (*Z*)-3-iodovinyl esters into pyranones was proposed (Scheme 6). Initially, the mechanism could take place through the formation of Pd(0) species followed by Pd(0) catalysis to produce intermediate **4**. This intermediate is further transformed into the cyclization product in the presence of ICl via iodocyclization.



Scheme 6. Proposed mechanism.

Conclusion

In summary, we have described an efficient synthesis of novel trisubstituted *2H*-pyran-2-ones bearing an amino group from *N*-substituted (*Z*)-3-iodovinyl esters via a one-pot sequence involving Sonogashira coupling and iodocyclization. This simple procedure might allow further functionalization at the 6 position of the *2H*-pyran-2-ones. Further utilization of this procedure in synthetic and pharmaceutical chemistry are currently underway in our laboratory.

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17. CCDC 1942651 contains the supplementary crystallographic data for **5a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data/_request/cif.

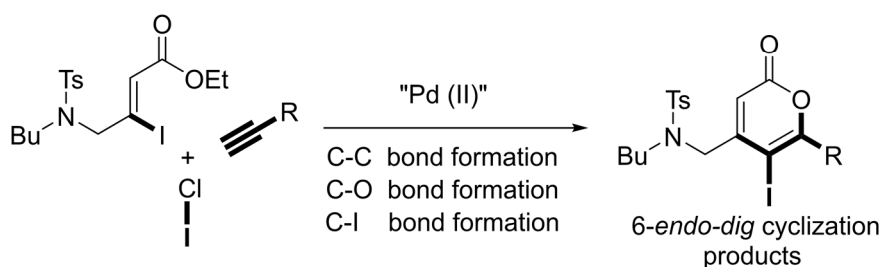
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- one-pot procedure
- inexpensive alcohol solvents
- 66-86% yield
- highly regio-controlled

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