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Synthesis of isocoumarins and α-pyrones via iodocyclization

Tuanli Yao and Richard C. Larock*

Department of Chemistry, Iowa State University, 2751 Gilman Hall, Ames, IA 50011, USA

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Abstract—A variety of 3-substituted 4-iodoisocoumarins and 6-substituted 5-iodo-2(2*H*)-pyranones are readily prepared in excellent yields under mild reaction conditions by the reaction of *o*-(1-alkynyl)benzoates and (*Z*)-2-alken-4-ynoates with ICl.

Isocoumarins[1] and α-pyrones[2] are useful intermediates in the synthesis of a variety of carbocyclic and heterocyclic compounds, including isocarbostyrils, isoquinolines, isochromenes, pyridones, and various aromatic compounds. These lactones also occur as structural subunits in numerous natural products that exhibit a wide range of biological activities, such as antimicrobial,[3] androgen-like,[4] phytotoxic,[5] antifungal[6] and pheromonal[7] effects. Very recently, low molecular weight α-pyrones have been shown to be potent HIV-1 protease inhibitors.[8]

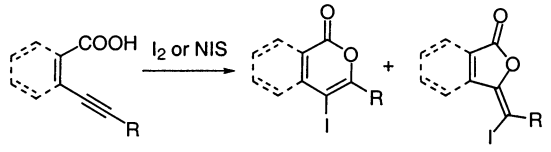
Traditional approaches to the synthesis of isocoumarins[9] and pyrones[10] have been diverse and a number of organometallic approaches have been reported over the past few years.[7,11] However, few very general procedures have thus far been developed. Previous workers have reported the synthesis of isocoumarins[12] and 5,6-disubstituted 2(2*H*)-pyranones[13] by the iodolactonization of 2-(1-alkynyl)benzoic acids and 5-substituted (*Z*)-2-alken-4-ynoic acids, respectively. Unfortunately, they have always obtained mixtures of 5- and 6-membered ring products (Scheme 1).

Oliver and Gandour have reported the bromolactonization of two alkyl 2-(2-phenylethynyl)benzoates.[14] Unfortunately, the scope of this cyclization has not been further examined (Scheme 2).

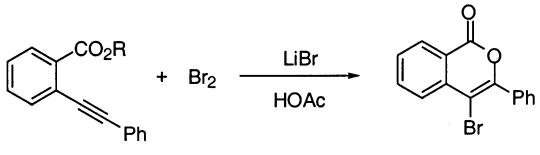
Recently, efficient syntheses of benzo[*b*]thiophenes,[15] isoquinolines[16] and naphthyridines[16] by electrophilic cyclization have been developed. Our interest in extending this type of cyclization prompted us to reexamine the synthesis of isocoumarins and α-pyrones (Scheme 3). Herein, we wish to report that electrophilic cyclization using the corresponding *ester*-containing alkynes and ICl provides a very regioselective method for the synthesis of isocoumarins and α-pyrones.

The *o*-(1-alkynyl)benzoates and (*Z*)-2-alken-4-ynoates required for our approach are readily prepared by Sonogashira coupling of the corresponding iodo compounds with terminal alkynes (Scheme 4). The yields from this process range from 90 to 100% and this procedure readily accommodates considerable functionality.

We first examined the reaction of our ester alkynes **1** and **3** (0.3 mmol in 3 ml of CH_2Cl_2) with ICl (1.2 equiv. in 0.4 ml of CH_2Cl_2) (Table 1, entries 1 and 2).[17] We were pleased to see that these substrates reacted in less than 30 min at room temperature with ICl to afford the



Scheme 1.



Scheme 2.

Keywords: isocoumarins; α-pyrones; iodocyclization.
* Corresponding author. Tel.: +1-515-294-4660; fax: +1-515-294-0105; e-mail: larock@iastate.edu

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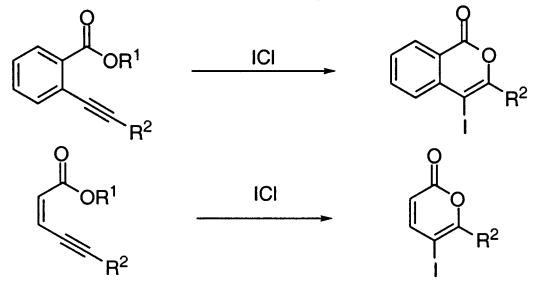
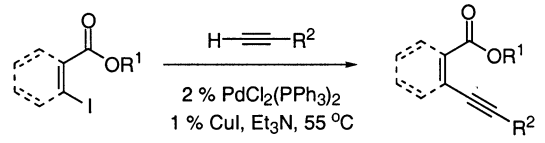


Scheme 3.

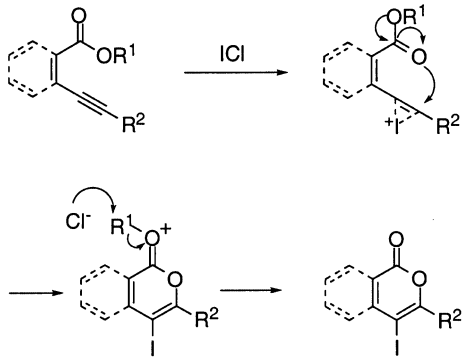


Scheme 4.

desired isocoumarins **2** and **4** in 90% and 85% isolated yields, respectively. The corresponding five-membered ring lactones were not observed in either case. Virtually no difference in the rate of reaction or the overall yield was observed using an alkyne bearing an aryl group (**1**) or a long chain alkyl group (**3**).

To further test the scope of this electrophilic cyclization, alkynes bearing functional groups, including silyl (**5**), vinylic (**7**), and hydroxy (**9**) groups, have been allowed to react with ICl. We were pleased to find that the alkyne bearing a Si(*i*-Pr)$_3$ group (**5**) reacted with ICl at room temperature to afford the corresponding 4-iodoisocoumarin **6**[18] in 96% yield. However, a mixture of the desired isocoumarin **8** and an unidentified byproduct was observed when the alkyne bearing a vinylic group (**7**) was allowed to react with ICl at room temperature. Interestingly, when the same reaction was carried out at −78°C, the desired 4-iodoisocoumarin **8** was the only product formed in 98% yield. The alkyne **9** bearing a hydroxy group also afforded the corresponding 4-iodoisocoumarin **10**, but only in moderate yield. Although no major sideproducts were obtained in this later reaction, it is possible that cyclization of the alcohol onto the carbon–carbon triple bond may be lowering our overall yield. We also have examined the reaction of the substituted *o*-(1-alkynyl)benzoate **11** with ICl (entry 6). Since electron-rich aryl groups might potentially react with ICl, we carried out this reaction at −78°C and were pleased to find that the desired 4-iodoisocoumarin **12** was the only product formed in a 99% isolated yield.

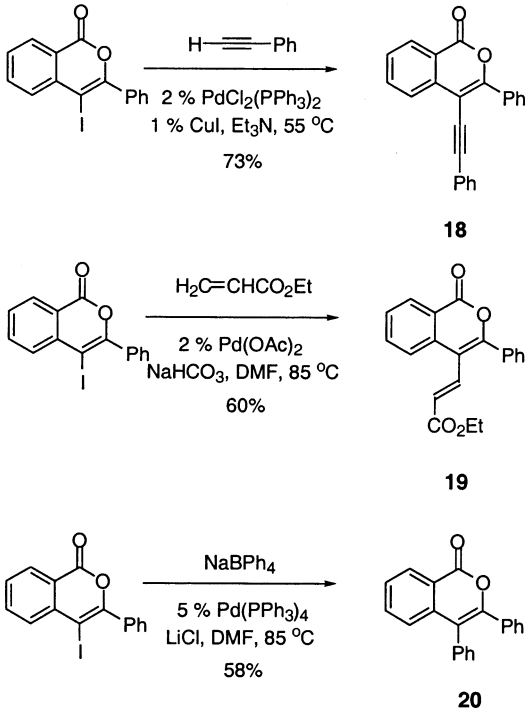
Surprisingly, the nature of the R^1 group of the ester had very little effect on the reaction rate or product yield. Even a *tert*-butyl ester (**13**) cyclized in approximately the same time and yield as the corresponding methyl ester (**1**) (compare entries 1 and 7). Based on this observation, we propose the following mechanism for this electrophilic cyclization (Scheme 5). Nucleophilic attack of the oxygen of the carbonyl group on the carbon–carbon triple bond activated by coordination to I$^+$ is followed by either S_N2 attack of the chloride on the R^1 group when R^1 = Me or perhaps S_N1 cleavage of the R^1 group in the case of the *t*-butyl ester.



Scheme 5.

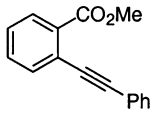
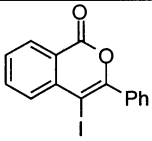
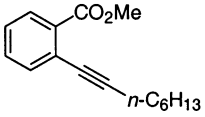
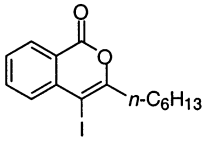
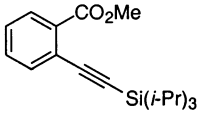
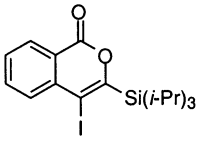
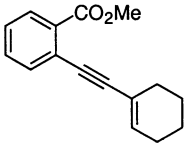
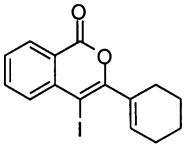
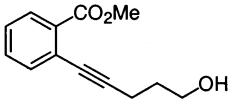
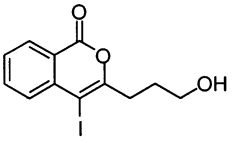
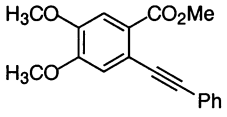
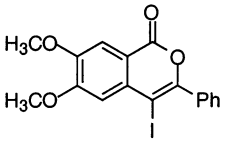
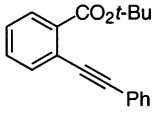
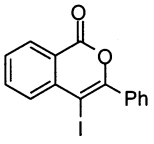
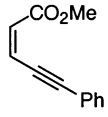
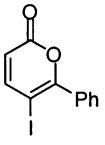
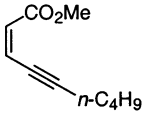
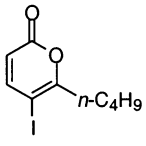
An interesting feature of this chemistry is the fact that the iodoisocoumarins and iodo-2(2*H*)-pyranones can be further elaborated using a variety of palladium-catalyzed processes. For example, the Sonogashira coupling reaction,[19] Heck reaction,[20] and Suzuki reaction[21] afforded the corresponding products **18**, **19** and **20** in 73%, 60% and 58% yields, respectively (Scheme 6).

In conclusion, efficient syntheses of 3-substituted 4-iodoisocoumarins and 6-substituted 5-iodo-2(2*H*)-pyranones under very mild reaction conditions have been developed. This methodology is successful with a variety of ester alkynes and affords the anticipated substituted isocoumarins and α-pyrones in excellent yields, free of the corresponding 5-membered ring lactones. Further investigation into the scope and limitations of this novel electrophilic cyclization is underway.



Scheme 6.

Table 1. Synthesis of substituted isocoumarins and α-pyrones[a]

Entry	Ester alkyne		Product		% Isolated yield
1		**1**		**2**	90
2		**3**		**4**	85
3		**5**		**6**	96
4		**7**		**8**	98[b]
5		**9**		**10**	51
6		**11**		**12**	99[b]
7		**13**		**2**	99
8		**14**		**15**	94
9		**16**		**17**	80

[a] See reference 17 for the experimental procedure. [b] The reaction was run at –78 °C.

Acknowledgements

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17. A representative procedure for synthesis of the isocoumarins and α-pyrones follows: the ester alkyne (0.30 mmol) in 3 ml of CH_2Cl_2 was placed in a 4 dram vial and flushed with N_2. The ICl (1.2 equiv.) in 0.5 ml of CH_2Cl_2 was added dropwise to the vial by a syringe. The reaction was stirred at room temperature for 30 min. The reaction mixture was then diluted with 50 ml of ether, washed with 25 ml of satd $Na_2S_2O_3$, dried ($MgSO_4$) and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column. See Ref. 18 for representative spectral data.
18. Isocoumarin **6**: purification by flash chromatography (20:1 hexane/EtOAc) afforded 123.6 mg (96%) of the product as a white solid: mp 117–120°C; ^{1}H NMR ($CDCl_3$) δ 1.13–1.23 (m, 18H), 1.63–1.74 (m, 3H), 7.65 (dt, J=0.9, 7.5 Hz, 1H), 7.79 (dt, J=1.2, 8.1 Hz, 1H), 7.95 (d, J=7.5 Hz, 1H), 9.18 (d, J=8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 18.9, 84.8, 125.8, 126.5, 127.1, 131.1, 134.3, 139.2, 153.1, 165.9; IR (neat, cm^{-1}) 2946, 2866, 1784; HRMS calcd for $C_{18}H_{25}IO_2Si$: 428.0668. Found: 428.0676.
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